INTENSIVE LOCOMOTOR-RELATED SKILL TRAINING AND TDCS NEUROMODULATION TO IMPROVE WALKING AND BALANCE FUNCTION IN PERSONS WITH CHRONIC SPINAL CORD INJURY

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Nicholas H. Evans

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Approved by:

Dr. Edelle C. Field-Fote, Advisor
School of Biological Sciences
Georgia Institute of Technology

Dr. Young-Hui Chang
School of Biological Sciences
Georgia Institute of Technology

Dr. T. Richard Nichols, Co-Advisor
School of Biological Sciences
Georgia Institute of Technology

Dr. Bradley J. Farrell
T3 Laboratories, Inc.
Global Center for Medical Innovation
Georgia Institute of Technology

Dr. Melinda L. Millard-Stafford
School of Biological Sciences
Georgia Institute of Technology

Date Approved: July 14, 2023

This dissertation is dedicated to the many individuals whose stories and experiences following spinal cord injury have inspired me to never stop seeking answers to questions that matter.

This work is dedicated to my daughter, Sydney N. Evans. Your presence in the world opened my eyes to the endless depths and vastness of love in the human heart. May you never be content with living in a *'tensionless state'* but rather live in a condition of striving for a worthwhile goal that will bring you joy and meaning.

This book is dedicated to the memory of my father, Scott D. Evans, who lost his battle with cancer in April, 2013. I am grateful and honored to have learned so much from you. Your life impressed upon me the power of a kind and encouraging word. And, also to my stepfather, Alexander 'Skip' Gossman, who passed away tragically in a motor vehicle accident in August, 2012. I am grateful for your unconditional and unwavering support.

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LIST OF SYMBOLS AND ABBREVIATIONS

2MWT	2-minute walk test
10MWT	10-meter walk test
ACC	angular component of the coefficient of correspondence
AEs	adverse events
AIS	ASIA impairment scale
ASIA	American Spinal Injury Association
tDCS	transcranial direct current stimulation
BBS	Berg Balance Scale
BDNF	brain-derived neurotrophic factor
BMI	body mass index
CNS	central nervous system
CPGs	central pattern generators
D1	Day 1, baseline
D2	Day 2, intervention session 1
D3	Day 3, intervention session 2
D4	Day 4, intervention session 3
D5	Day 5, 24-hours post-intervention
FES-I	Falls Efficacy Scale-International
GXT	graded exercise test
HR_{avg}	average heart rate
HR_{peak}	peak heart rate
HRR	heart rate reserve

IMU	inertial measurement unit
ISNCSI	International Standards for Neurological Classification of Spinal Cord Injury
LEMS	lower extremity motor score
MCID	minimal clinically important difference
MEP	motor evoked potential
MISCI	motor incomplete spinal cord injury
MLR	mesencephalic locomotor region
MST	motor skill training
$MST+tDCS_{sham}$	motor skill training plus sham transcranial direct current stimulation
MST+tDCS	motor skill training plus active transcranial direct current stimulation
NLI	neurological level of injury
NMDA	N-methyl-D-aspartate
PwMISCI	persons with motor-incomplete spinal cord injury
PwSCI	persons with spinal cord injury
rTMS	repetitive transcranial magnetic stimulation
SCATS	Spinal Cord Assessment Tool for Spastic Reflexes
SCI	spinal cord injury
SF	step frequency
SL	stride length
STL	step length
SI	symmetry index
tDCS	transcranial direct current stimulation
TLA	trailing limb angle
TMS	transcranial magnetic stimulation

TrkB	tropomyosin-related kinase B
TSI	time since injury
TSS	transcutaneous spinal stimulation
VO_{2peak}	peak oxygen consumption
WR	walk ratio
WS	walk speed

SUMMARY

Spinal cord injury (SCI) results in immediate and persistent impairments in sensory and motor function below the neurological level of injury. Improved walking function is a priority among persons with SCI (PwSCI), particularly among those with preservation of motor function below the level of injury. Rehabilitation strategies aimed at recovery of walking function in PwSCI are primarily directed toward activation of spinal neural networks despite evidence demonstrating that human bipedal locomotion involves both spinal and supraspinal contributions. Additionally, the cost and long-term accessibility of existing locomotor training approaches limits participation in ongoing training once individuals are discharged from the clinical setting. Consequently, training interventions aimed at enhancing corticospinal drive to motoneurons of the lower limb muscles and that can be feasibly carried out in the home or community setting, either with or without supervision, may be advantageous. These interventions may have value both for promoting long-term recovery of walking function beyond initial rehabilitation, and/or for preserving gains in walking function acquired during rehabilitation.

Considering the need to explore alternative interventions that can be feasibly implemented beyond initial rehabilitation and the need to develop interventions that expand the range of neural targets subserving bipedal walking, this thesis explores the following questions: (1) Do persons with motor-incomplete SCI (PwMISCI) demonstrate improvements in lower limb motor function and walking performance following an intensive, high-velocity locomotor-related motor skill training intervention?; (2) Does enhancing corticospinal drive through the addition of non-invasive brain stimulation,

delivered to the motor cortex and cerebellum, augment the effects of lower limb motor training in this population?; (3) Are there specific characteristics of walking performance that are most influenced by high-velocity locomotor-related motor skill training among PwMISCI?

In chapter 2 we compare the combined effects of three days of locomotor-related motor skill training alone versus motor training combined with transcranial direct current stimulation (tDCS). Individuals with motor-incomplete SCI were randomized to either a motor skill training plus sham tDCS condition (MST+$tDCS_{sham}$) or a motor skill training plus active tDCS condition (MST+tDCS). Measures of walking function and gait quality were collected over five consecutive days and between-groups differences in the cumulative effects of training were compared. Three consecutive days of MST was associated with significant improvements in walking speed, walking distance, and spatiotemporal gait characteristics (i.e., cadence, stride length); however, no differences in outcomes were observed between those who did and did not receive active neuromodulation using tDCS.

In chapter 3 we examined the within-day (online) and between-day (offline) effects of intensive MST on measures of walking and balance function over three consecutive days. We further examined whether MST combined with tDCS would lead to differences in within- and between-day changes in outcomes compared to MST alone. In addition to examining changes in walking performance, we measured the cumulative effects of MST on upright balance and perceived fear of falling. Participation in MST was associated with significant increases in overground walking speed, cadence, bilateral stride length, stronger limb trailing limb angle (TLA), and intralimb coordination of the weaker leg. However,

concurrent application of tDCS with MST was not associated with greater improvement in outcomes of interest compared to motor training alone. Measures of balance function and perceived fear of falling were also improved. Furthermore, among those walking outcomes that were positively influenced by MST intervention, between-day (offline) effects contributed to a greater proportion of total change in outcomes compared to within-day (online) effects.

In chapter 4 we characterize the step length-frequency relationship, in terms of the Walk Ratio, and examine the effects of MST on the interaction between changes in spatiotemporal measures subserving walking speed and changes in step length-frequency coordination in PwMISCI. Furthermore, we divide the study sample into slow versus fast walkers using cluster analysis to account for differences in outcomes that may be attributable to differences in walking speed. Given the diminished capacity to produce high step frequencies along with a relatively intact ability to modulate step length, we anticipated that higher Walk Ratio values (i.e., diminished step length-frequency coordination) would be observed among PwMISCI compared to previous reports in non-injured adults. Furthermore, we anticipated that MST emphasizing high-velocity lower limb movements would be associated with improvements in step length-frequency coordination mediated in large part by improvements in the capacity to increase SF. Among the full study sample, we observed higher Walk Ratio values among PwMISCI than previous reports in other neurological populations; however, values among fast walkers were comparable to non-injured adults. Slow walkers demonstrated greater variability in the Walk Ratio with higher values associated with slower walking speed. Following MST,

increases in walking speed among slow walkers coincided with a decrease in the Walk Ratio, mediated primarily through an effect on step frequency.

In chapter 5 we summarize the overall findings detailed in Chapters 2, 3, and 4 and discuss the clinical and scientific relevance of these observations. These include the observations that a brief intensive, high-velocity MST designed to overcome limitations of existing locomotor training approaches was effective at improving measures of overground walking function and balance in PwMISCI, that concurrent application of tDCS failed to augment the effects of MST, that between-day (offline) change in outcomes contributed to observed improvements to a greater extent than within-day (online) change, and that the high-velocity nature of MST may have contributed to improvements in walking speed through a greater effect on step frequency compared to step length. In addition, we consider methodological factors that could improve the quality of future studies and the interpretability of findings following paired motor training and tDCS. Finally, we present future considerations that could enhance our understanding of the potential mechanisms and effectiveness of the MST intervention for enhancing walking and balance function in PwMISCI.

CHAPTER 1. INTRODUCTION

1.1 Altered central nervous system morphology/physiology leads to impaired motor function following spinal cord injury

The spinal cord constitutes part of the central nervous system (CNS) and is comprised of longitudinally oriented tracts, intra-segmental neurons, and inter-segmental neural networks that lie within the vertebral column. The spinal tracts contain sensory and motor axons, with peripheral connections that enter and exit through the intervertebral space and make it possible for the brain, body systems, and organs to communicate. Damage to the neural elements within the spinal cord can have a profound effect on various body systems and can lead to partial or complete loss of motor, sensory, and/or autonomic nervous system function at and below the spinal cord lesion level. A spinal cord injury (SCI) can result from a traumatic event or non-traumatic pathology. Common causes of traumatic SCI include motor vehicle accidents, falls, violence, and occupational or sports injuries (National Spinal Cord Injury Statistical Center, 2023), while causes of non-traumatic SCI include congenital-genetic disorders (e.g. neural tube defects, skeletal malformations, hereditary spastic paraplegia) or acquired conditions (e.g. vertebral column degeneration, infectious disease, metabolic and vascular disorders, spinal tumors, inflammatory and auto-immune diseases) (New & Marshall, 2014).

The nature of impairments resulting from SCI are dependent on the level, location, and severity of the injury. Injuries to the cervical segments of the spinal cord (C1-C8) lead to tetraplegia with impairment or loss of motor and/or sensory function in the arms, trunk,

legs, and pelvic organs (bowel, bladder, sexual organs). Injuries to the thoracic (T1-T12), lumbar (L1-L5), or sacral (S1-S5) segments of the spinal cord lead to paraplegia with impairment or loss of motor and/or sensory function in the trunk, legs, and pelvic organs. Clinical examinations, such as the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (American Spinal Injury Association, 2015), are often administered to describe the neurological level and completeness of an injury and to provide a means by which standardized information concerning motor, sensory, and autonomic nervous system function can be communicated among health care providers and research scientists (American Spinal Injury Association, 2015). Based on examination results, it is standard clinical practice to assign an American Spinal Injury Association (ASIA) Impairment Scale (AIS) classification to indicate whether volitional motor function is present below the level of injury, wherein AIS A/B indicates no preserved motor function and AIS C/D/E indicates some or full motor preservation.

Globally, the annual incidence of SCI is estimated to be between 250,000 and 500,000 new cases (World Health Organization, 2013). In the United States, SCI is the second leading cause of paralysis with approximately 18,000 new cases occurring each year (Jain et al., 2015; National Spinal Cord Injury Statistical Center, 2023). Approximately 60% of SCI cases result in tetraplegia and 40% result in paraplegia (National Spinal Cord Injury Statistical Center, 2023). Although differences in the average age at injury exist between traumatic (15-29 years) and non-traumatic SCI (60-70 years), males continue to make up the majority of those who experience an SCI across injury types (Christopher & Dana Reeve Foundation, 2009; National Spinal Cord Injury Statistical Center, 2023; World Health Organization, 2013). Despite advances in emergency medical

management and acute and post-acute rehabilitative care, the life expectancy of PwSCI remains lower than the general adult population (Chamberlain et al., 2015; National Spinal Cord Injury Statistical Center, 2023; World Health Organization, 2013). The estimated lifetime costs of SCI range from approximately $2.8 million (paraplegia) to $5.8 million (tetraplegia), not including indirect costs associated with lost wages, benefits, and productivity (Devivo et al., 2011).

The pathophysiology of traumatic SCI is characterized by both primary and secondary injury mechanisms. Primary injury occurs as a direct result of trauma to the neural elements within the spinal cord and is marked by systemic and local events including plasma membrane compromise, cellular necrosis, spinal shock, hemorrhage, vasospasm, ischemia, hypoxia, derangements in ionic homeostasis, and accumulation of neurotransmitters (Steeves & Wu, 2015). These primary events often lead to a cascade of secondary traumatic responses including immune cell invasion and cytokine release, neuronal and glial apoptosis, glutamatergic excitotoxicity, demyelination of surviving axons above and below the site of injury, central cavitation, glial scar formation, and alteration of ion channels and receptors (Oyinbo, 2011). Interestingly, and germane to the immediate and long-term loss of motor function experienced by individuals with SCI, neuronal apoptosis is not a phenomenon restricted to the spinal cord at the level of injury but can occur along the entirety of the neuroaxis including at the level of pyramidal cells within the primary motor cortex (Hains et al., 2003).

Owing to the altered CNS morphology/physiology and subsequent loss of motor and sensory function, it is not surprising that PwSCI experience diminished muscular strength, compromised aerobic capacity, physical deconditioning, and loss of functional mobility,

including walking and balancing (Janssen et al., 2002; Simmons et al., 2014). Further compounding the problem of lost mobility are low exercise participation and increased sedentary time, which become more pervasive as the chronicity of injury increases (Martin Ginis et al., 2010; Rimmer et al., 2004). Additionally, involuntary muscle spasms, decreased cortical excitability, reorganization of sensorimotor maps, muscle atrophy, and alteration of muscle fiber type and composition (Biering-Sorenson et al., 2009; Davey et al., 1998; Freund et al., 2011; Gorgey & Dudley, 2007; Hoffman & Field-Fote, 2007) can significantly contribute to impaired functional capacity, decreased independence with activities of daily living, increased risk of cardiovascular and metabolic comorbidities, and decreased life expectancy (Chamberlain et al., 2015; Cowan & Nash, 2010; Sisto & Evans, 2014). Consequently, impaired motor function and physical deconditioning are major concerns for PwSCI and their health care providers.

Restoration of walking is cited as a priority among PwSCI, regardless of severity, chronicity, or age at injury (Simpson et al., 2012), yet the collective consequences of SCI have made it difficult to select the most appropriate and optimal targets for improving walking function following injury. Numerous therapeutic approaches involving cell therapies, pharmacology, electrical stimulation, combinatorial exercise interventions, and locomotor training strategies have been implemented in the hopes of improving motor function and walking-related outcomes in the SCI population (Gomes-Osman et al., 2016). However, studies aimed at improving walking function in PwSCI have focused primarily on activation of spinal circuits, despite considerable evidence demonstrating the contributions of supraspinal networks to animal and human locomotion (Armstrong, 1988; Yang & Gorassini, 2006).

1.2 The strength of corticospinal drive influences walking function

Bipedal locomotion is a complex motor behavior involving rhythmic sequences of muscle activity initiated by descending supraspinal inputs and maintained through activation of spinal central pattern generators (CPGs), integration of sensory information from the periphery and environment, and ongoing modulatory control from supraspinal networks (Capaday, 2002; Nielsen, 2003). Over four decades of research in pre-clinical models of SCI have revealed significant contributions of spinal CPGs to the production and ongoing maintenance of the basic motor patterns underlying locomotion (Barriere et al., 2008). The observation that quadrupedal patterned locomotion on a treadmill can be produced in the absence of descending supraspinal input has informed the development of rehabilitation approaches aimed at the recovery of walking after SCI (Guertin, 2014; Torres-Espin et al., 2018). While in pre-clinical models of CNS injury spinal CPGs can generate cyclic, alternating lower limb movements in the absence of major descending cortical contributions (Barriere et al., 2008; Gottschall & Nichols, 2007; Sherrington, 1910), supraspinal inputs play a necessary and important role in achieving coordinated, functional walking in both animals and humans (Artoni et al., 2017; Jahn et al., 2008; Mori et al., 1978; Orlovsky, 1972). More specifically, the planning, execution, and maintenance of locomotion depends on the contribution of multiple cortical and subcortical regions including the basal ganglia, mesencephalic locomotor region (MLR), cerebellum, supplementary motor area, premotor area, and the primary motor cortex (Drew & Marigold, 2015; Takakusaki, 2017). Functional bipedal walking depends upon the direct and indirect projections from these structures to spinal circuits and motoneurons of muscles

involved in stepping and maintenance of postural equilibrium (Artoni et al., 2017; Peterson et al., 2012).

The motor cortex exerts direct modulatory control over the ankle dorsiflexor and plantarflexor muscles on a step-by-step basis via the corticospinal neural network (Peterson et al., 2001). In this way, corticospinal drive not only serves to modify the pattern of spinal CPGs but also functions to precisely control foot placement in situations where there are constraints or obstacles present in the walking environment (Beloozerova & Sirota, 1993; Krouchev & Drew, 2013). Consequently, corticospinal tract integrity is necessary for optimal gait control in human walking, and damage to the neural elements within the corticospinal tract can lead to decreased corticospinal drive (Barthelemy et al., 2015), diminished inhibitory modulation of reflex excitability (Kumru et al., 2010), and impaired volitional motor function (Awai et al., 2016), all of which contribute to pathological gait in the SCI population.

Although the corticospinal tract is a primary pathway for volitional lower limb motor control, initiating and sustaining upright walking requires ongoing integration of sensory information and descending input from many other key supraspinal centers. For example, locomotion is also influenced by descending input from vestibulospinal and reticulospinal pathways. Specifically, these pathways subserve spinal reflex modulation, control of axial muscle tone, and maintenance of postural equilibrium and lower limb coordination (Barthelemy et al., 2015; Brownstone & Chopek, 2018; Witts & Murray, 2019), which are necessary features of upright stability and motor control during bipedal walking. Neuroanatomically, reticular formation and vestibular nuclei receive inputs from numerous motor control centers including the motor cortex, cerebellum, and MLR.

Sensory information concerning activity of spinal CPGs and position of lower limb segments is conveyed to the cerebellum through spinocerebellar pathways that modulate Purkinje cell spike activity (Armstrong & Edgley, 1984), which in turn leads to modulation of deep cerebellar nuclei (e.g., dentate and interpose nuclei) and ensuing effects on motor integration centers including the thalamus, basal ganglia, and reticular formation (Grillner & El Manira, 2020). Through this neural circuitry, the cerebellum monitors and modifies ongoing locomotor activity, particularly in cases where perturbations or obstacles are encountered during stepping (Andersson & Armstrong, 1987).

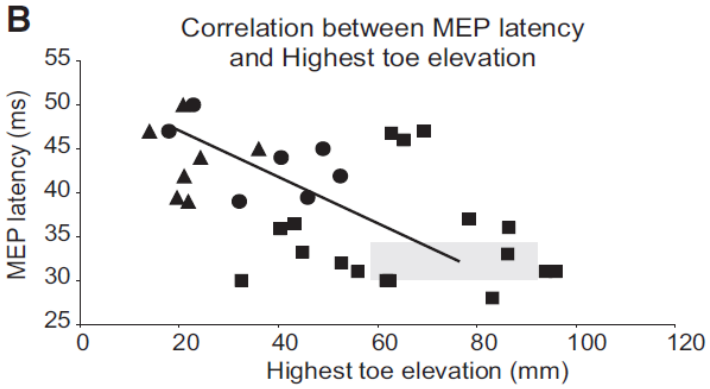
In response to persistent, coupled inputs, cerebellar neurons undergo permanent neuroplastic change (Hull, 2020), which in turn change cerebellar outputs. Afferent inputs arriving from motor and sensory systems alter Purkinje cell simple and complex spike firing rates leading to intrinsic (Jang et al., 2023) and synaptic (Tanaka et al., 2013) changes in the primary output cells of the cerebellum. Coupled arrival of parallel fiber and climbing fiber inputs onto the same Purkinje cell suppresses simple spike firing frequency resulting in disinhibition of deep cerebellar nuclei (De Zeeuw & Brinke, 2015). These outputs make the cerebellum an important supraspinal center that contributes to motor learning. Long-term depression of Purkinje cells through coupled neural inputs is believed to be the primary mechanism by which integrated neural feedback facilitates the acquisition and consolidation of motor patterns in the cerebellum (Hirano, 2013).

Additionally, the MLR is a notable region in the midbrain associated with initiating and modulating the timing of spinal CPG activity (Sherman et al., 2015; Skinner & Garcia-Rill, 1984). In fact, pre-clinical and clinical studies have highlighted the unique contribution of descending reticulospinal inputs originating from the MLR to functional

quadrupedal and bipedal walking. In decerebrate cats, electrical stimulation of the MLR is capable of inducing coordinated hindlimb or quadrupedal locomotion, depending on the degree of preserved postural tone (Mori et al., 1978; Opris et al., 2019).When MLR stimulation is paired with cerebellar stimulation to produce treadmill walking, the magnitude and duration of lower limb muscle bursting activity is increased (Mori et al., 1999). This suggests an integrated link between the two locomotor control centers that is capable of amplifying the motor response during locomotion, either through direct connections between the MLR and cerebellum (Vitale et al., 2016) or through convergence of multiple descending reticulospinal inputs onto spinal motoneurons (Mori et al., 1999). Lesions of the MLR in humans are associated with impaired standing balance and gait ataxia despite preserved lower limb muscle strength considered to be within a normal range (Hathout & Bhidayasiri, 2005; Masdeu et al., 1994). In older adults with grey matter atrophy of the MLR but no other signs of neurological injury or disease, gait initiation and postural control are disrupted leading to walking and balance impairments (Demain et al., 2014). Considering the contributions of the MLR along with those of the cerebellum, it is evident that functional walking is a complex motor task involving multiple supraspinal structures and descending pathways; however, damage to the corticospinal tract in PwSCI appears to be a primary contributing factor to gait deficits in this population.

Studies using transcranial magnetic stimulation (TMS) to excite the motor cortex have revealed that PwSCI exhibit cortically evoked motor responses with delayed latencies, higher stimulus thresholds, and decreased amplitudes compared to non-injured controls (Davey et al., 1998; Smith et al., 2000). These neurophysiological findings are correlated with functional outcomes, where the capacity to recover walking function is

dependent upon the extent to which spared supraspinal pathways remain intact (Field-Fote et al., 2016). For example, the latency of the motor-evoked potential (MEP) response of the tibialis anterior is negatively associated with the ability to modulate ankle dorsiflexion during the swing phase of walking (Barthelemy et al., 2010), and the MEP magnitude of the same muscle is significantly correlated with clinical measures of functional walking capacity (see Figure 1.1) (Barthelemy et al., 2015). Given the important role that supraspinal centers play in the planning, execution, and ongoing maintenance of lower limb movements during bipedal locomotion and the relationship between the strength of descending inputs and walking performance, supraspinal centers that contribute to corticospinal drive and locomotor control are logical targets for promoting recovery of walking after SCI (Oudega & Perez, 2012).



	6-Min Walk Test	Timed-Up and Go	Walking Index Spinal Cord Injury	Gait speed
MEP latency	−0.361 (0.13)	0.256 (0.3)	−0.298 (0.22)	−0.440 (0.07)
MEP amplitude	**0.584 (0.02)**	**−0.417 (0.12)**	**0.572 (0.03)**	**0.496 (0.07)**

Figure 1.1. Figure depicting a negative association between the latency of the tibialis anterior motor-evoked response and the magnitude of toe elevation during the swing phase of walking among persons with SCI (From: Barthelemy et al., J Neurophys 2010). Data below the figure indicates significant associations between the magnitude of the motor-evoked response of the tibialis anterior and measures of walking function (From: Barthelemy et al., Prog Brain Res 2015)

1.3 Motor training increases corticospinal drive and improves motor function

In the late 1980's, locomotor training strategies for PwSCI began to emerge that were based on pre-clinical evidence in animals with complete spinal transection that targeted spinal pattern generating networks (Barbeau & Rossignol, 1987; Barbeau et al., 1987; Hubli & Dietz, 2013; Werning & Muller, 1992). However, there has been growing interest in the role of training approaches aimed at activating spared corticospinal pathways to enhance recovery of function following injury (Field-Fote et al., 2016). Specifically, volitional repetitive task practice as a means of promoting descending corticospinal drive has garnered increased attention. Preliminary evidence in healthy adults indicates that voluntary, repetitive (Perez et al., 2004) and high velocity (Beck et al., 2007) ankle dorsiflexion training is associated with enhanced corticospinal excitability, as evidenced by an increase in the amplitude of the tibialis anterior MEP following training. Additional evidence involving more complex motor tasks indicates that repetitive stepping during treadmill training leads to increased maximum MEP responses of the tibialis anterior and vastus lateralis muscles among PwSCI and that these increases are positively associated with improvements in walking capacity (see Figure 1.2) (Thomas et al., 2005).

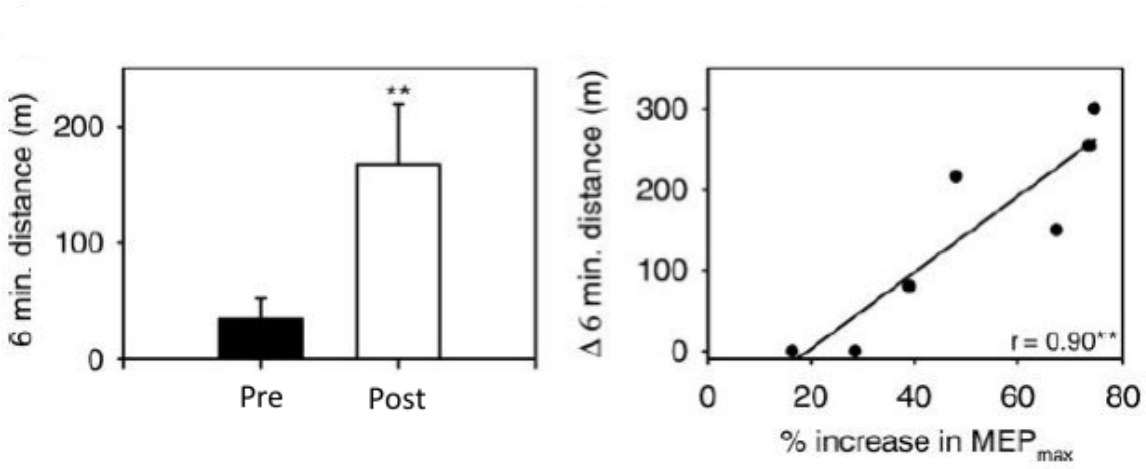


Figure 1.2. Association between increased corticospinal drive (as measured by maximal tibialis anterior MEP response) and walking capacity following treadmill training in PwSCI (From: Thomas et al., J Neurophys 2005).

Further support for the value of increasing corticospinal drive to facilitate recovery of function in PwSCI has been provided by members of our own laboratory, in which it was demonstrated that a high repetition motor training program led to improvements in both muscle activation and walking function (Manella et al., 2013). Participants in the study were randomized to one of two operant conditioning training programs; one to increase voluntary ankle dorsiflexor control and the other to decrease ankle plantarflexor stretch reflex excitability. In both conditions, participants completed a total of 3600 repetitions of the assigned training task over a 5-week period. Differences in volitional muscle activation of the tibialis anterior, reflex modulation of the soleus, and spatiotemporal measures of walking function were compared between groups. Although both groups demonstrated significant within-group improvements in 2-minute walking distance following training, only the group that emphasized increased ankle dorsiflexion activation demonstrated significant improvements in active ankle dorsiflexion range of motion, toe clearance during walking, and volitional strength of the ankle dorsiflexor

muscles. Taken as a whole, the above findings indicate that a focus on increasing volitional activation may have a more meaningful influence on motor control and function than an emphasis on decreasing reflex excitability. Furthermore, the evidence supports the plausibility that lower extremity motor function can be improved through targeted motor training by altering the level of excitability within the corticospinal neuroaxis and by increasing the activation of spared descending pathways in PwSCI. A summary of the neurophysiological and functional outcomes referenced in the above literature is provided in Table 1.1.

Table 1.1. Summary of neurophysiological and functional outcomes following motor training in neurological populations.

OUTCOMES:	TREADMILL TRAINING	ANKLE DORSIFLEXION TRAINING
↑ corticospinal drive	•	•
↑ ankle dorsiflexion strength	•	•
↑ active ankle dorsiflexion ROM		•
↑ walking speed		•
↑ walking distance	•	•

Abbreviation: Range of Motion (ROM)

1.4 Non-invasive brain stimulation improves effectiveness of motor training

Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been employed with the aim of directly facilitating or inhibiting cortical networks to induce neuroplasticity, enhance motor performance and learning, and augment the effects of motor skill training (Page et al., 2015). Evidence suggests that combining motor training with

brain stimulation increases corticospinal drive by raising the level of excitability of targeted neural networks. While both rTMS and tDCS are thought to produce neuromodulatory effects on motor-cortical excitability, they differ in distinct ways in their application and proposed mechanisms of action.

RTMS evokes a motor response in the target muscles, while tDCS increases or decreases excitability of the underlying neurons without evoking a motor response. With respect to rTMS, the technique often involves placing a circular or figure-8 coil on the head and delivering repeated magnetic pulses that induce an electric field in the brain. The stimulation coil size, geometry, and placement, as well as the pulse parameters, determine the electric field distribution and the focality of excitability induced across targeted brain regions. Repetitive TMS provides higher temporal and spatial resolution, which is an advantage in experiments that probe neurophysiologic effects on specific brain circuits. Pharmacological studies have revealed that the higher resolution of rTMS produces its neuromodulatory effect through direct excitation and depolarization of cortico-cortical (measured in terms of motor threshold) and corticospinal (measured in terms of MEP amplitude) axons (Ziemann et al., 2015).

In healthy adults, rTMS applied to the primary motor cortex during a sequential finger movement task improved target accuracy and movement speed compared to sham stimulation (Y. Kim et al., 2004). In a sham-controlled, randomized crossover study in participants with chronic tetraplegia conducted by members of our own lab, functional task practice training for hand dexterity combined with rTMS delivered to the hand representation area of the motor cortex resulted in clinically meaningful improvements in hand function compared to sham stimulation (Gomes-Osman & Field-Fote, 2015b).

Furthermore, this change was observed in both the trained and untrained hands, suggesting crossover effects. The combination of brain stimulation and motor training was also associated with increased grasp strength and increased excitability of corticospinal circuits associated with the trained muscle, as evidenced by increased amplitude of the MEP. Finally, in a study investigating the effects of rTMS on lower extremity function in PwSCI, fifteen days of rTMS delivered to the leg representation area of the motor cortex prior to gait training was associated with improved lower extremity motor function and increased walking speed compared to sham stimulation (Figure 1.3) (Benito et al., 2012). Despite these promising results, rTMS poses limitations that restrict its widespread use in clinical and community settings. For instance, TMS technology is costly, it requires considerable time and training to be used reliably, and it cannot be delivered consistently when combined with more dynamic, upright motor training activities such as walking, standing balance, or jumping.

In contrast to rTMS, tDCS involves fixation (with an elastic band or cap) of two or more saline-soaked or gel surface electrodes on the scalp. A current is passed through the brain, entering via an anodal (positive) electrode and exiting through a cathodal (negative) electrode, which generates an electric field that is directly proportional to the current delivered (Paulus et al., 2013). According to both animal and human observations, the consensus is that tDCS produces its effects through modulation of neuronal membrane potentials, spontaneous neuronal activity, and cortical excitability, but not by means of direct elicitation of action potentials in underlying neural structures (Fertonani & Miniussi, 2017).

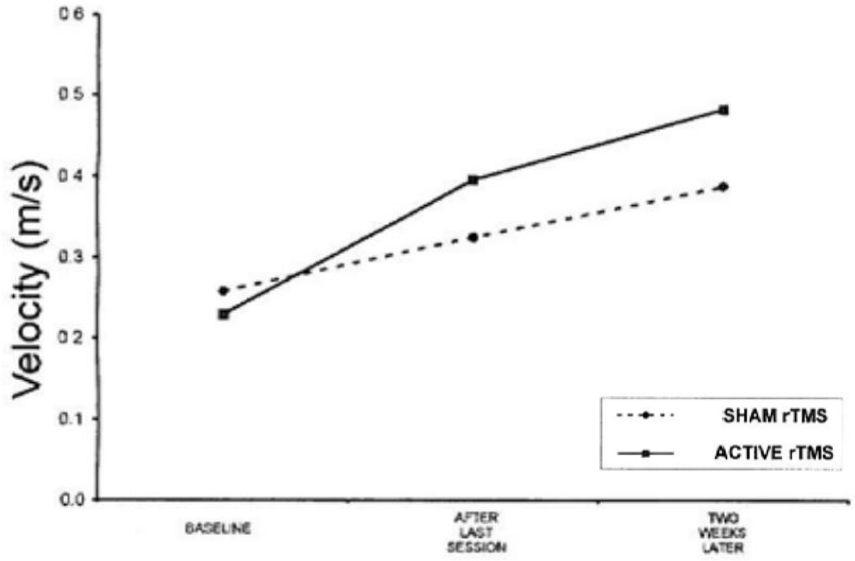


Figure 1.3. Immediate and persistent improvements in overground walking velocity following 15 sessions of combined rTMS (delivered to the motor cortex) and overground walking training among persons with motor-incomplete spinal cord injury. (From: Benito et al., *Top Spinal Cord Inj Rehabil*, 2012)

When the anodal electrode is placed over a target brain region, neural excitability is facilitated. According to neurophysiological evidence, anodal-tDCS delivered to the primary motor cortex (M1) leads to increased corticospinal drive to target muscles of the extremities, as evidenced by an increase in the motor-evoked response induced by TMS (Madhaven & Stinear, 2010). In contrast, when the cathodal electrode is applied over a target brain region, a decrease in neural excitability (i.e., inhibition) is observed, as evidenced by a reduction in the motor-evoked response induced by TMS (Nitsche, Nitsche, et al., 2003). Therefore, depending on the location of the anodal and cathodal electrodes, tDCS can modulate the level of excitability of underlying neurons by influencing membrane potentials and the probability of eliciting action potentials in response to endogenous (Nitsche et al., 2007) or exogenous stimulation (Kaski et al., 2012; Kronberg et al., 2020). For instance, cathodal-tDCS delivered to the cerebellum suppresses Purkinje

cell spiking activity (Zhang et al., 2021) leading to disinhibition of deep cerebellar nuclei and increased excitatory outflow to the M1 via the thalamo-cortical pathway (Celnik, 2015; Galea et al., 2009). Anodal-tDCS delivered to the M1 increases motor cortical excitability and enhances corticospinal drive to muscles of the lower extremities (Jeffery et al., 2007). When cathodal-cerebellar tDCS is combined with anodal-M1 tDCS, the magnitude of the motor-evoked response generated by motor cortical TMS is greater than that generated by anodal-M1 tDCS alone (Kaski et al., 2012).

When tDCS is applied prior to or concurrently with a training task, the approach is referred to as "priming". TDCS neuromodulation induces immediate changes in neural excitability through activation of sodium, potassium, and calcium channels (i.e., *gating*) (Vasu & Kaphzan, 2021, 2022a, 2022b), as well as more delayed changes in postsynaptic excitability through NMDA receptor activation (i.e., *homeostatic plasticity*), specifically in layer V neurons of the cerebral cortex (Nitsche, Fricke, et al., 2003; Stoykov & Madhaven, 2015). Both NMDA receptor and calcium channel activation increases intracellular calcium levels and leads to downstream signaling cascades that facilitate the upregulation and expression of neurotrophins, such as brain-derived neurotrophic factor (BDNF) (Cocco et al., 2018).

BDNF is a member of the neurotrophin family of growth factors that facilitates various developmental and functional events within the central nervous system. BDNF binds to the high-affinity cell membrane receptor tropomyosin-related kinase B (TrkB), and depending on the number of TrkB receptors expressed on cell membranes and the mode of BDNF exposure, BDNF/TrkB signaling regulates neuronal cell survival, dendritic growth, synapse formation, and inhibitory-excitatory neuronal balance (Guo et al., 2014;

Guo et al., 2018; Yoshi & Constantine-Paton, 2009). From a clinical perspective, the proposed effects and practical characteristics of tDCS offer a cost-effective, accessible means of neuromodulation that can be easily combined with dynamic motor skill activities during clinical practice. A summary of key distinctions between rTMS and tDCS is provided in Table 1.2.

Table 1.2. Key differences between rTMS and tDCS.

Stimulation Paradigm	Cost	Sham Stimulation	Penetration Depth	Focality	Online Stimulation During Complex Motor Tasks	Evoked Motor Response
tDCS	Low	Easily Concealed	Low	Low	Easily Administered	Subthreshold
rTMS	High	Difficult to Conceal	High	High	Difficult to Administer	Sub- or Suprathreshold

As described above, tDCS is a technology that delivers low-intensity currents to brain regions of interest with the aim of modulating neuronal excitability without generating action potentials. TDCS is less costly and lacks many of the feasibility limitations of rTMS, making it more accessible in clinical practice. There are a number of studies in which tDCS has been employed to augment upper extremity motor training in persons with stroke (Elsner et al., 2017); however, far fewer studies investigating the efficacy of combined motor training and tDCS have been conducted in the SCI population. In a randomized crossover study conducted by members of our lab, it was demonstrated that a single session of tDCS delivered to the primary motor cortex combined with functional task practice training for hand dexterity was successful at augmenting the effectiveness of training in individuals with cervical level SCI (Gomes-Osman & Field-Fote, 2015a). In fact, of the various stimulation approaches that were employed to increase

motor cortical activation, the findings indicated that, compared to focal tendon vibration and peripheral nerve stimulation, tDCS had the greatest effect on all three outcomes of interest – finger strength, hand strength gradation, and manual dexterity (Figure 1.4). Despite evidence supporting the functional benefits of combined tDCS and upper limb motor training, intra- and inter-individual responsiveness to tDCS appears to be highly variable (Horvath et al., 2016; Lopez-Alonso et al., 2015; Vergallito et al., 2022) and far less evidence is available concerning the effects of tDCS on lower limb motor function.

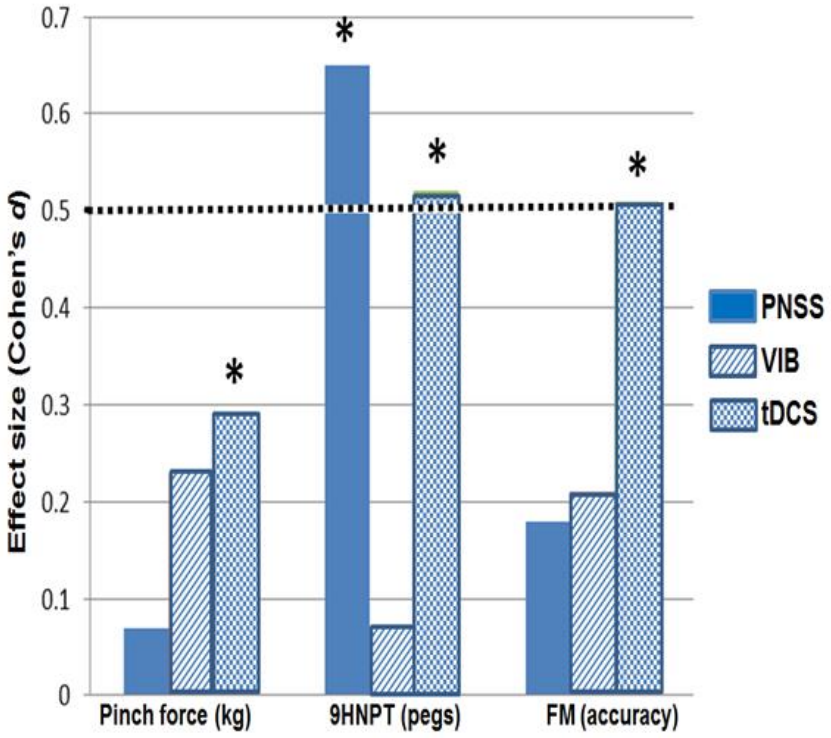


Figure 1.4. A single session of tDCS is associated with meaningful effects on upper extremity motor function.

Note: Change in pinch force, Nine-hole Peg Test (9HPT), and pinch force modulation (FM) following a single session of peripheral nerve somatosensory stimulation (PNSS), vibration (VIB), or transcranial direct current stimulation (tDCS). tDCS was associated with significant effects on all measures (asterisks (*); $p \leq 0.05$). Dashed line indicates threshold for moderate effect size. (From: Gomes-Osman & Field-Fote. *J Neuro Phys Ther* 2015)

To date, only three studies in persons with stroke and two studies in PwSCI have combined tDCS with lower extremity motor training. Among persons with stroke, significant improvements were observed in outcome measures of interest including increased dorsiflexor control (Madhaven et al., 2011), enhanced lower limb strength (Sohn et al., 2013; Tanaka et al., 2011), and improved upright balance (Sohn et al., 2013). Among PwSCI, walking function improved following robotic-assisted treadmill training but neither study reported differences in walking performance between those that received tDCS and those that received sham stimulation (Kumru et al., 2016; Raithatha et al., 2016). It is important to note that both of these studies employed robotic-assisted treadmill training, only one study delivered tDCS concurrently with training (Kumru et al., 2016), and neither study applied stimulation to both the primary motor cortex and cerebellum.

These are important distinctions, because the type of training, the timing of tDCS application, and targets of stimulation may have important implications for the effectiveness of these combined approaches. For example, robotic-assisted gait training is often considered a more passive, lower-intensity form of motor training when compared to activities that require continuous intensive, volitional effort to achieve a desired outcome (i.e., over-ground walking). Furthermore, although there remains no universal agreement on the question of stimulation timing, there is evidence that tDCS applied concurrently with an ankle dorsiflexion training task produced greater improvements in ankle motor control compared to stimulation applied before the training task (Sriraman et al., 2014). Finally, prior evidence indicates that anodal-tDCS delivered to the leg representation area of the primary motor cortex and cathodal-tDCS delivered to the cerebellum increases corticospinal drive to muscles of the lower extremities to a greater extent than anodal-tDCS

to the motor cortex alone (Kaski et al., 2012). It is currently unknown what benefits could be derived from combined M1-cerebellar tDCS and lower limb motor training that involves intensive volitional effort, but it is plausible, given the existing evidence in the upper limb, that motor skill training to improve lower limb muscle activation could be enhanced by the addition of tDCS.

1.5 Intensity of exercise effects motor skill performance and promotes neuroplasticity

Virtually all acquired motor behaviors involve some element of skill learning, increased muscular strength, and increased endurance that develop through practice (Adkins et al., 2006). Motor skill learning involves exposure to new movement patterns, integration of muscle synergies, and consolidation of new movement sequences in the form of motor memories (Reis et al., 2008). These concepts are of particular importance in rehabilitation programs where strategies to optimize the acquisition and retention of motor skills are necessary to facilitate long-term restoration of function following injury (Roig et al., 2012). Although the mechanisms underlying functional restoration are multifactorial, evidence indicates that motor skill training induces synaptic changes in cortical and spinal circuitry resulting in increases in synaptic strength of active circuits and reorganization of neural ensembles that encode movement in the motor cortex (Brown & Martinez, 2019; Kida & Mitsushima, 2018; Kida et al., 2016). Furthermore, it is widely accepted that the nature of this neural adaptation and reorganization, through Hebbian processes, is dependent upon the specific demands of the training experience (Adkins et al., 2006). As

a result, careful consideration has been given to the effect of manipulating the training demands in order to improve motor skill performance and optimize recovery following injury.

Research in stroke and SCI supports the efficacy of high repetition, task-specific motor skill training for the restoration of function and relearning of complex motor tasks (Boyona et al., 2005; Yang & Musselman, 2012). More recently, evidence has pointed to the *intensity* of training as an additional critical factor in promoting neuroplasticity and improving motor function following injuries to the nervous system (Leech & Hornby, 2017; Mang et al., 2016; Rojas Vega et al., 2008). In fact, evidence indicates that activities performed at moderate- to high-intensity may yield greater neuromotor benefits compared to those performed at low-intensities. Support for this assertion has centered around several mechanistic concepts, such as changes in cerebral blood flow (Singh & Staines, 2015), increased glucocorticoid (Milani et al., 2010) and neurotrophin (He et al., 2013) release, and altered states of arousal (McMorris et al., 2015).

The phenomenon of learning and performance and their association with training intensity has spanned multiple scientific domains. In the fields of psychology, physiology, and neuroscience, it has been observed that the relationship between task performance and stimulus intensity follows an inverted-U pattern, where intensities that are either too low or too high generally fail to correspond to optimal levels of learning, memory consolidation, and performance. This relationship suggests that exposure to stimuli of increasing intensity produces, through various mechanisms, a more favorable neurobiological environment that optimizes particular features of human performance and learning (McMorris et al., 2015; Yerkes & Dodson, 1908). Generally, the hypothesis is that

low intensity stimuli fail to sufficiently activate the systems necessary to optimize performance and memory consolidation, while very high intensity stimuli result in overstimulation or inhibition of these systems. A model of the inverted-U relationship is illustrated in Figure 1.5. Several related physiological phenomena follow an inverted-U pattern and provide mechanistic evidence for the possibility of an intensity-dependent effect of exercise on neuromodulation and neuroplasticity.

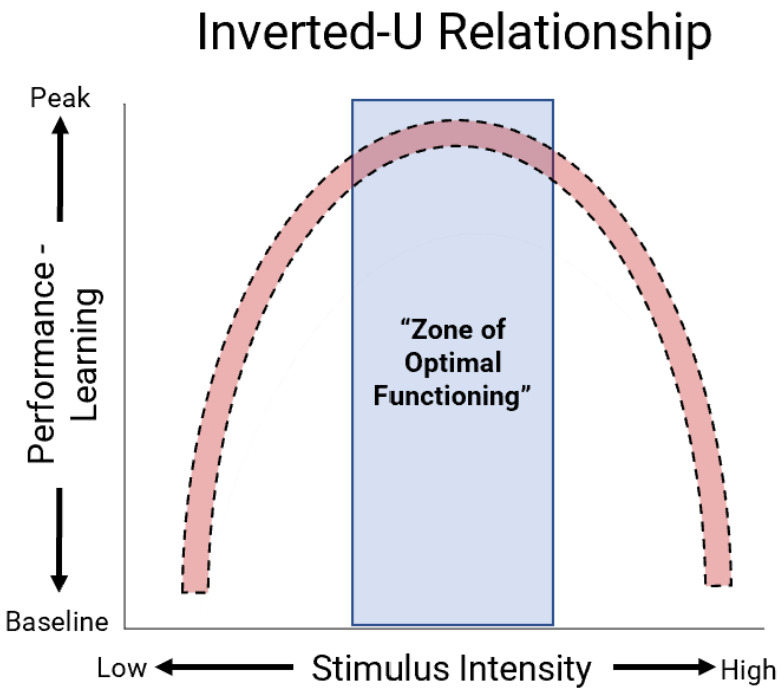


Figure 1.5. Motor performance and learning are optimized when intensity is neither too low nor too high. (Yerkes & Dodson. *J Comp Neuro Psych* 1908; McMorris et al., *Physiol Behav* 2015)

First, regional cerebral blood flow increases in the primary motor cortex, primary somatosensory cortex, and supplementary motor area in response to aerobic exercise (Singh & Staines, 2015). For example, cerebral blood flow through the middle cerebral arteries that supply the motor cortices increases with cycling exercise, peaks at approximately 60% of maximal oxygen consumption (VO_{2max}), progressively declines, and then plateaus as the exercise intensity approaches 100% of maximal aerobic capacity

(Moraine et al., 1993). This observation is significant insofar as blood flow provides the necessary neuronal energy substrates (e.g., glucose and lactate) needed to facilitate functional processes within the brain that support the performance of motor activities and the neuronal interactions required for motor memory consolidation (i.e., Hebbian-type learning).

Second, exercise represents a physical stressor, which stimulates the hypothalamic-pituitary-adrenal axis leading to secretion of cortisol from the adrenal cortex. As the intensity of exercise increases, so too does circulating blood cortisol, where significant increases in basal cortisol levels are observed when exercise intensities reach 40-60% of VO_{2max} and continue to rise as exercise intensities approach maximal levels of exertion (Hill et al., 2008). Cortisol readily crosses the blood-brain barrier and binds to both mineralocorticoid and glucocorticoid receptors within the CNS. Cortisol-receptor binding within the CNS influences both long-term potentiation and long-term depression within neuronal networks that underlie learning and memory processing (Andreano & Cahill, 2006; de Kloet et al., 1999). For example, mineralocorticoid and glucocorticoid receptors are highly expressed in the motor cortex and hippocampus, and the extent of cortisol binding to these two receptors gives rise to differential effects. During moderate-intensity exercise, blood cortisol concentrations rise and high affinity mineralocorticoid receptors become fully saturated while low affinity glucocorticoid receptors become only partially saturated. Complete binding of mineralocorticoid receptors with only partial binding of glucocorticoid receptors is associated with increased synaptic plasticity leading to long-term potentiation (de Kloet et al., 1999; Lupien et al., 2007). In contrast, when blood cortisol concentrations reach higher levels (as is the case under severe stress such as during

prolonged high-intensity exercise), glucocorticoid receptor binding increases, and this increase is associated with impaired induction of long-term potentiation and facilitation of long-term depression within the CNS (Dinse et al., 2017; Tatomir et al., 2014). These distinct cortisol-receptor interactions provide mechanistic support for an intensity-dependent effect of exercise on motor learning and the consolidation of motor programs within the CNS.

Finally, and of particular interest among persons with neurologic conditions, the intensity-dependent and systemic upregulation and release of BDNF in the periphery and in the CNS is considered the primary effect of exercise on motor learning, memory formation, and enhanced motor performance (Cobianchi et al., 2017; Dinoff et al., 2016; Inoue et al., 2018; Mang et al., 2014; McDonnell et al., 2013; Phillips et al., 2014; Skriver et al., 2014). Primary sources of BDNF appear to reside in the brain and circulating thrombocytes, although BDNF is expressed in other tissues such as skeletal muscle and vascular endothelium (Walsh & Tschakovsky, 2018). The release of BDNF from these sites is thought to occur in response to excitatory synaptic activity within the CNS as well as platelet shear stress and thrombin activation (via protease-activated receptor-1) associated with sustained physical exercise (Fujimara et al., 2002; Tamura et al., 2011; Walsh & Tschakovsky, 2018). With respect to its role in motor performance and motor learning, BDNF messenger RNA is extensively distributed in motor-related neurons within the cerebellum, basal ganglia, brain stem, and spinal cord (He et al., 2013).

In recent years, there has been significant interest in identifying the conditions under which concentrations of BDNF can be increased endogenously. Despite methodological differences in BDNF sample collection and analysis, two recent meta-

analyses confirm that exercise performed with sufficient intensity can lead to a significant increase in BDNF (Dinoff et al., 2016; Szuhany et al., 2015). These increases have been linked to improved performance outcomes in healthy adults, wherein an increase in plasma BDNF following a single bout of intense cycling was positively correlated with greater retention of an upper extremity motor task (Skriver et al., 2014). Furthermore, in animal models, moderate- but not high-intensity exercise is associated with increases in BDNF and hippocampal neurogenesis (So et al., 2017), while blockade of BDNF expression during exercise abolishes the positive effects of exercise on memory and learning (Intlekofer et al., 2013). In persons with neuropathology, the relationship between exercise, BDNF, and performance outcomes is less clear, primarily due to a limited number of studies investigating such interactions as well as the high variability in responsiveness to training (Mackay et al., 2017). However, of the few studies that have been published, exercise of at least moderate-intensity is necessary to induce measurable changes in serum concentrations of BDNF. For example, 30-minutes of moderate-intensity but not low-intensity walking led to an increase in serum BDNF in participants with chronic stroke (de Morais et al., 2018). Additionally, moderate-intensity hand-cycling produced an increase in serum BDNF that was greater than both rest and high-intensity cycling in athletes with chronic SCI (Rojas Vega et al., 2008). Despite what appears to be a positive association between exercise and increased circulating BDNF, it is still unclear to what extent changes in peripheral concentrations of BDNF relate to improvements in motor performance in persons with neuropathology.

It is clear that intensity-dependent effects of exercise on physiological processes directly modify CNS activity and function. It is plausible that these mechanisms contribute

to ‘fine-tuning’ and stabilization of Hebbian processes that support motor skill acquisition and consolidation (Bilchak et al., 2021). This may be accomplished through direct activation of motor circuits specifically involved in a particular motor task or by indirectly altering the level of excitability of motor control networks that respond to incoming sensory information, thereby increasing the probability of network integration with additional activation (Hebb, 1949). In either case, the mechanisms underlying the relationship between exercise intensity, motor performance, and acquisition are highly complex and likely involve the interaction of a number of physiological processes that have yet to be disentangled.

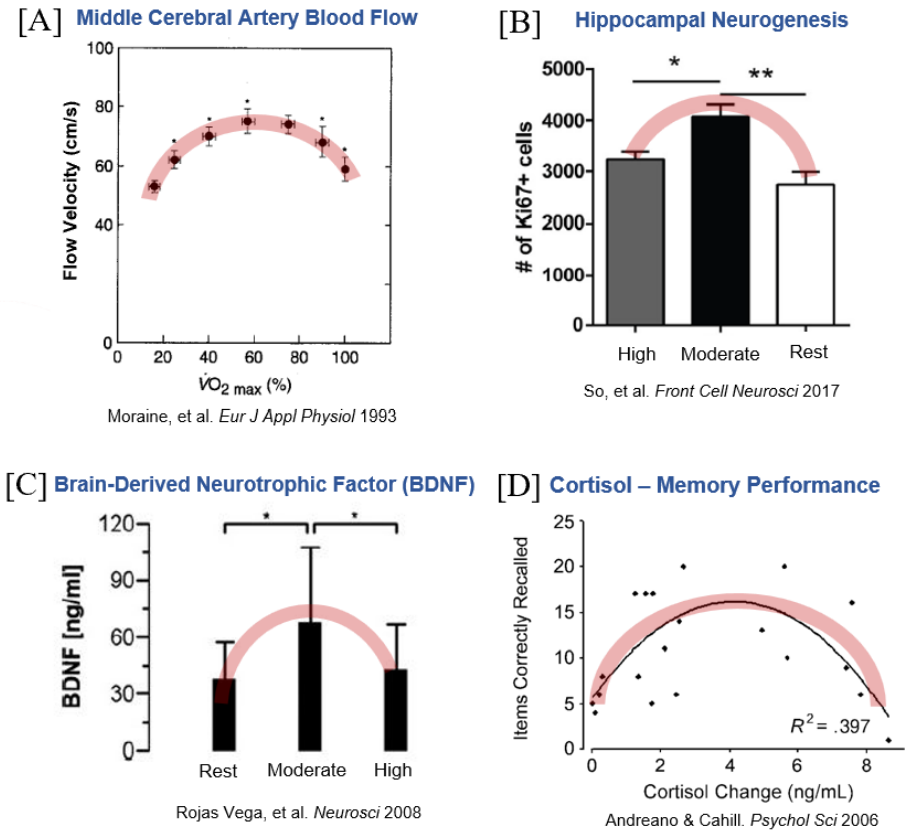


Figure 1.6. Exercise intensity-dependent physiological responses demonstrating inverted-U relationships. [A] MCA blood flow velocity and $\%VO_{2max}$. [B] Moderate-intensity exercise associated with significant increase in hippocampal neurogenesis. [C] Increased circulating BDNF following moderate- but not high-intensity exercise. [D] Memory consolidation optimized with moderate levels of circulating cortisol.

1.6 Broader research significance and clinical implications

Although the number of persons affected by SCI may be relatively small compared to other neurological conditions such as stroke and acquired brain injury (approximately 18,000 new cases in the United States each year (National Spinal Cord Injury Statistical Center, 2023)), many PwSCI are young adults who can expect to live with disability for 40 – 50 years. Consequently, in terms of disability-years, the potential long-term impact of discovering and selecting the most useful rehabilitation strategies for PwSCI is large. The following dissertation has broad significance in that: 1) it provides preliminary evidence as to whether a combination of treatment strategies can lead to greater improvements in rehabilitation outcomes, which have the potential to enhance quality of life over the lifespan, and 2) it provides evidence that could have clinical relevance for persons with motor impairments resulting from other forms of neuropathology.

Strategies to optimize rehabilitation outcomes: This dissertation will explore the value of priming neural circuits using non-invasive brain stimulation to improve walking function in PwSCI. This exploration is motivated by the belief that the key to optimizing rehabilitation outcomes is the development of therapies that extract the greatest benefits from the limited time available for rehabilitation. Restoration of walking function is cited as a priority among PwSCI of all degrees of severity, chronicity, and age at injury. Given the functional and health-related value of standing and walking and the fact that many PwSCI are injured as young adults, even small improvements in walking function can have a significant impact on health, quality of life, and social participation after SCI. For example, being able to stand and walk through a narrow doorway, to negotiate confined spaces inaccessible by wheelchair, or to get out of a wheelchair to sit in a “regular” chair

at a table with friends provides opportunities to participate in the world in ways that might otherwise be unattainable. With this in mind, the primary focus of the research detailed in this dissertation was to positively impact one of the most fundamental features of human experience, namely, upright functional walking.

Significance for other clinical populations: In addition to the above, this dissertation has broader implications in that the neuropathology underlying deficits of walking function following SCI are similar in many ways to those underlying other chronic central nervous system disorders such as stroke, multiple sclerosis, cerebral palsy, and traumatic brain injury. Therefore, identifying optimal combinatorial rehabilitation strategies to improve walking function would be of value not only to those with SCI but also to those with mobility impairments caused by other neurological conditions. The research detailed in this dissertation may be of additional significance in that the findings have the potential to move the field of neurorehabilitation forward by identifying complementary interventions that promote restoration of walking function across the various communities of neurologic conditions.

CHAPTER 2. A PILOT STUDY OF INTENSIVE LOCOMOTOR-RELATED SKILL TRAINING AND TRANSCRANIAL DIRECT CURRENT STIMULATION IN CHRONIC SPINAL CORD INJURY

2.1 Introduction

Restoration of walking is a priority among persons with motor-incomplete spinal cord injury (PwMISCI) (Simpson et al., 2012). Walking speed, as a metric of walking function, is a common target in SCI rehabilitation and is predictive of community independence following injury (van Hedel & Group, 2009; van Silfhout et al., 2017). Although locomotor training that emphasizes high repetitions of stepping has beneficial effects on neurophysiological outcomes in pre-clinical SCI models (Dietz, 2009), this training (Barbeau et al., 1987; Hannold et al., 2006) has been associated with only modest improvements in functional walking in human SCI (Dobkin & Duncan, 2012; Merholz et al., 2017; Morawietz & Moffat, 2013; Smith & Knikou, 2016). Moreover, this approach has other limitations. Locomotor training is restricted to centers where technology and therapist assistance is readily available, such that access (Singh et al., 2018) and cost (Jones et al., 2012) limit long-term participation. Interventions that target locomotor deficits and that can be carried-out in the home or community are likely to confer greater long-term benefits on walking function.

Although task-specificity is an important feature of transferability of motor skill training (Bayona et al., 2005), other motor learning principles deserve consideration in

designing interventions to optimize walking function after SCI. In a recent randomized crossover study, impairment-based training, involving muscle strengthening, balance, and cardiorespiratory exercise, was not found to be superior to combined treadmill and overground locomotor training for improving walking function in PwMISCI (Lotter et al., 2020). However, neither speed of movement nor functional relevance of the impairment-based tasks were considered as part of the training approach. Propulsive impulse and peak ground reaction force at push-off are diminished in PwMISCI and are correlated with a reduction in walking speed (Peters et al., 2018). Repetitive, ballistic motor training, involving rapid, volitional force production, increases corticomotor-evoked responses in muscles of the lower extremities (Beck et al., 2007; Perez et al., 2004) and enhances rate of motor unit recruitment compared to activities involving low force, low velocity contractions (Del Vecchio et al., 2019; Van Cutsem et al., 1998; Wallace & Janz, 2009). Motor training that requires little to no technology/equipment and that emphasizes rapid force generation within a context that is functionally relevant to features of overground walking, such as rapid ankle dorsiflexion, brisk limb alternation, and explosive propulsion, could provide an effective alternative to locomotor training.

Recent findings emphasize the importance of training *intensity* as a means of influencing neuroplasticity and improving motor function in persons with neurologic conditions (Leech & Hornby, 2017; Mang et al., 2016; Rojas Vega et al., 2008). Activities performed at moderate- to high-intensity appear to yield greater neuromotor benefits than those performed at low-intensities (Brazg et al., 2017; Fisher et al., 2008; Hasan et al., 2016; Leech et al., 2016). In non-injured adults, a single session of moderate-intensity exercise has been found to promote motor skill acquisition (Statton et al., 2015),

presumably through neurotrophic mechanisms believed to facilitate a variety of neuroplastic events within the nervous system (Guo et al., 2014; Guo et al., 2018; Yoshi & Constantine-Paton, 2009). Training approaches that capitalize on the effects of intensive activity may have potential for meaningful impact on motor function, including walking, in PwMISCI.

Beyond the importance of repetition, task-specific muscle recruitment, and activation of neuroplastic processes, motor learning depends on engaging the most relevant neural circuits. Most studies aimed at improving walking function in PwMISCI have followed guidance from early studies of locomotor training that emphasized activation of spinal circuits (Behrman & Harkema, 2000). However, there is robust evidence demonstrating the important contributions of supraspinal networks to animal and human locomotion (Armstrong, 1988; Yang & Gorassini, 2006). For example, through the corticospinal network, the motor cortex exerts direct modulatory control over the ankle dorsiflexor and plantarflexor muscles on a step-by-step basis (Meyer et al., 2020; Peterson et al., 2001). For this reason, there is value in exploring strategies that increase corticospinal drive to the spinal circuits. Non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS), modulates excitability of cortical networks thereby increasing corticospinal activation (Page et al., 2015). TDCS is thought to "prime" neural circuits and thereby enhance training effects (Sriraman et al., 2014). Several prior studies by our lab and others have investigated tDCS for augmenting upper extremity training in persons with tetraplegia (Cortes et al., 2017; Estes et al., 2017; Gomes-Osman & Field-Fote, 2015a; Potter-Baker et al., 2018; Yozbatiran et al., 2016). Only two studies in PwMISCI have assessed tDCS combined with lower extremity training (Kumru et al.,

2016; Raithatha et al., 2016). Both used robotic-assisted treadmill training, and neither identified significant differences in walking function (i.e., walking speed) with tDCS intervention. The neuromodulatory benefits of tDCS are dependent upon the specificity (Kronberg et al., 2020) and strength (Kronberg et al., 2017) of endogenous synaptic inputs present at the time of stimulation. Although robotic-assisted treadmill training promotes repetitive stepping, it is often relatively passive (Fenuta & Hicks, 2014; Kressler et al., 2013), imposes constraints on movement, and does not allow users the opportunity to actively explore their capacity to correct movement errors (Field-Fote & Roach, 2011), which are obstacles to optimizing motor learning (Emken et al., 2007; Mutha et al., 2011) and may limit the effectiveness of tDCS neuromodulation.

In line with recommendations for the progressive development of larger randomized clinical trials (Dobkin, 2009), the purpose of this Phase II pilot study was to examine the efficacy of a locomotor-related motor skill training (MST) intervention. Further, as the rehabilitation research community has been urged to test combinational strategies "to create a more formidable intervention" (Dobkin, 2009) to improve walking function, we sought to determine whether the MST intervention combined with tDCS had greater efficacy. The specific aims were to examine whether moderate-intensity MST improved walking function in PwMISCI and whether augmenting training with tDCS influenced outcomes. We hypothesized that MST would be associated with improvements in walking function and gait quality and that tDCS in conjunction with MST would lead to greater improvements than MST alone.

2.2 Methods

2.2.1 Study design and regulatory oversight

In a parallel group design, participants were randomized to one of two groups ([1] MST with concurrent sham tDCS (MST+tDCS$_{sham}$) or [2] MST with concurrent tDCS (MST+tDCS)) based on a computer-generated randomization table (REDCap randomization module) created by staff not otherwise involved in the study. Both the participants and the assessor were blinded to group allocation. The study was carried-out over five consecutive days, with assessments on the first day (Monday [D1; baseline] and last day (Friday [D5]; 24-hours post-intervention), and interventions on the middle three consecutive days (Tuesday [D2], Wednesday [D3], Thursday [D4]). Single-session effects on motor function have been reported for tDCS (Tanaka et al., 2011). When administered on consecutive days, tDCS leads to greater cumulative effects on corticospinal excitability compared to stimulation delivered second daily (Alonzo et al., 2012). A three consecutive day intervention was selected based on the above observations in order to establish preliminary evidence of efficacy prior to undertaking a longer study. A subset of assessments were performed on intervention days; here we examine cumulative effects from D1 to D5.

The study protocol, including the off-label use of the tDCS device, was approved by the Institutional Review Board at Shepherd Center in Atlanta, GA in accordance with the Declaration of Helsinki. The study was registered prior to enrollment of the first participant (ClinicalTrials.gov: NCT03237234). All participants provided written informed consent.

2.2.2 Study sample

Sample size was estimated based on changes in walking speed in participants with SCI, wherein an effect size of 0.69 was identified (Manella et al., 2013). With α=0.10 and power=0.80, a sample size of 15 participants/group was determined to identify significant differences in walking speed (G*Power 3.1: F tests, ANOVA repeated measures, between-factors). Criteria for participation were: (a) chronic MISCI (≥12 months) at/above the T10 neurological level, (b) aged 18-70 years, (c) able to stand for ≥5 minutes, (d) able to advance each leg independently ≥3 steps, and (e) able/willing to provide consent. Exclusion criteria were: (a) progressive spinal lesions, (b) uncontrolled cardiorespiratory condition, (c) altered cognitive status, (d) orthopedic pathology, (e) intracranial metal, (f) history of seizures. American Spinal Injury Association Impairment Scale (AIS) classification and lower extremity motor scores (LEMS) were obtained from participant medical records (if assessed within prior 6-months) or following neurological examination by a member of the research team.

2.2.3 Interventions

2.2.3.1 Motor skill training (MST)

The MST circuit included activities of importance for walking function. Targeted muscle groups included the knee extensors/flexors, hip extensors/flexors, and ankle plantar/dorsiflexors. The relative strength of these muscle groups is predictive of walking performance in PwMISCI (Crozier et al., 1992; C. Kim et al., 2004; van Middendorp et al.,

2011; Wirth et al., 2008a). Six activities were selected, organized into a circuit (Figure 2.1), and repeated 4 times/session. Participants were instructed to "*complete as many repetitions as possible in 60 seconds as quickly as possible, while maintaining appropriate form*". The intent of this design was to create a circuit that would take approximately 30 minutes to complete, including transition time between activities, and that would require, at minimum, a sustained moderate-intensity effort. The duration and training intensity selected are consistent with current clinical practice guidelines for the development and implementation of locomotor training interventions in persons with neurologic conditions (Hornby et al., 2020). MST activities incorporated cyclic (repetitive, alternating lower limb motions) (Vietnen & Welch, 2020) and/or ballistic (high rate of force development) (Cordner et al., 2021) movements. Cyclic lower limb movement is a characteristic feature of human locomotion, while rapid lower limb force production, particularly in the ankle plantar flexors, hip flexors, and hip extensors, is important for forward propulsion and walking speed modulation (Peters et al., 2018; Peterson et al., 2011). Activities were selected that incorporated task-specific movement goals, could feasibly be performed in a home/community setting, that challenged upright balance, and promoted rapid activation/deactivation of targeted muscle groups.

Activities #1-5 emphasized active lower extremity range of motion, upright balance, and rapid, cyclic activation/deactivation of muscles involved in propulsion. Activity #6 emphasized rapid, cyclic ankle dorsiflexion and was the only seated activity, which provided opportunity for active rest prior to restarting the circuit. Modification was provided as needed to ensure each participant could complete all activities. Some participants were permitted to grasp a fixed bar for balance support if standing was unsafe.

Eleven participants were provided manual assistance by the interventionist in cases where they were unable to independently bring their foot to the step (activity #2). In cases where participants lacked sufficient force-generating capacity to achieve vertical jump (activity #4), they were simply instructed to rapidly accelerate from the squat position in an attempt to leave the ground.

Heart rate was monitored continuously throughout the MST circuit (Polar FT1, Polar Electro Inc., NY, USA). Verbal cueing was provided to encourage participants to perform activities rapidly with the aim of maintaining at least moderate exercise intensity (i.e., 40-60% heart rate reserve [HRR]). Target intensity thresholds were calculated from resting and peak heart rate (HR_{peak}) obtained during baseline upper body (Monark Exercise AB, Vansbro, Sweden) graded-exercise testing (GXT). Maximal GXT procedures and termination criteria followed accepted practices (*ACSM's Guidelines for Exercise Testing and Prescription*, 2018). Average heart rate (HR_{avg}) and HR_{peak} were recorded for each MST session.

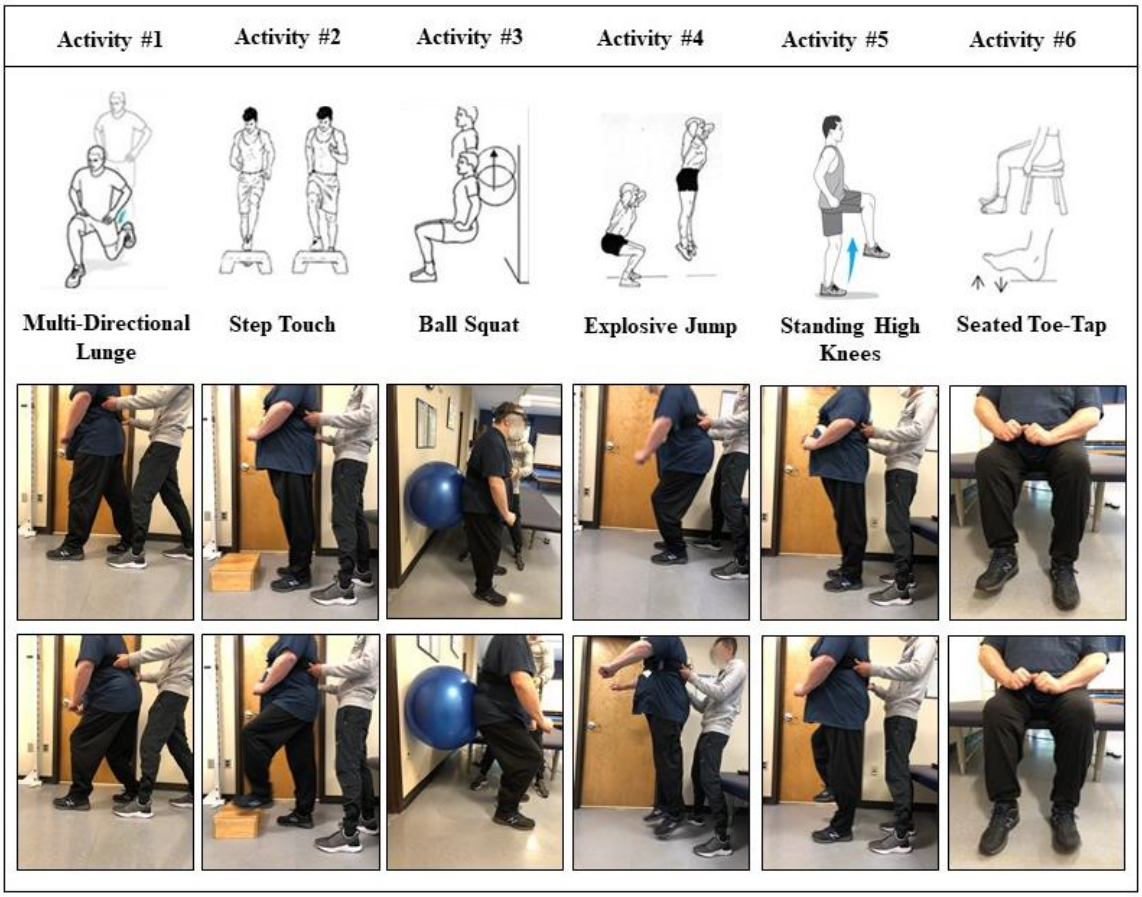


Figure 2.1. Locomotor-related motor skill training (MST) circuit involving cyclic, ballistic volitional movement sequences. Top row: Image sketch of each activity. Middle and bottom rows: Images of a representative participant, with a baseline total lower extremity motor score = 31 and overground walking speed = 0.54m/s, completing each activity with contact guard assist provided by the interventionist.

2.2.3.2 Transcranial direct current stimulation (tDCS)

Anodal tDCS (2mA; ActivaDose II, Activa Tek Inc., CA, USA) was delivered concurrently with MST for 20-minutes using two, 5x5cm 0.9% saline-soaked electrodes. The calculated current density (0.80 A/m^2) and charge density (0.96 kC/m^2) were within safety guidelines for tDCS (Bikson et al., 2009; Chhatbar et al., 2017). The anode was placed slightly anterior to the vertex (targeting bilateral M1 cortices), and the cathode was placed at the inion (targeting the cerebellum) (Figure 2.2) (Kaski et al., 2012). Prior

evidence indicates that these parameters and electrode montage are associated with increased M1 activation of lower extremity muscles (Kaski et al., 2012) and improved locomotor and balance performance in healthy adults (Kaski et al., 2012), as well as persons with gait and balance dysfunction (Kaski et al., 2013). Electrodes were secured using elastic head straps with notations for reproducibility of positioning and were monitored for placement throughout MST. The MST+tDCS$_{sham}$ group had identical set-up procedures; however, at the start of each session, stimulation was ramped-up to 2mA then ramped-down to 0mA over a period of approximately 40-secs (Kaski et al., 2012). A member of the research laboratory not involved in outcomes testing or MST delivery administered tDCS. Personnel who delivered MST and performed outcomes testing were blinded to the stimulation condition.

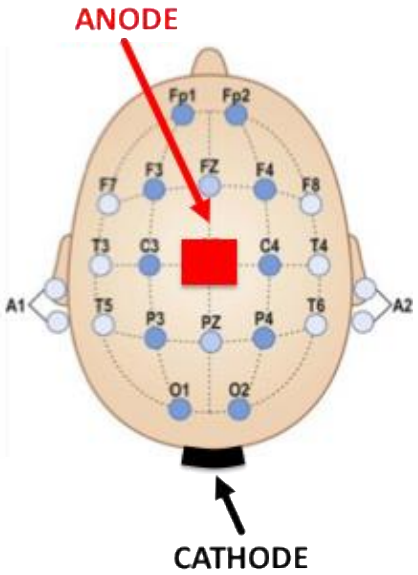


Figure 2.2. Transcranial direct current stimulation (tDCS) electrode montage with the red box indicating the positively charged anode electrode over M1 and the black box indicating the negatively charged cathode electrode over the inion.

2.2.4 Outcome measures

2.2.4.1 Walking Function

Walking speed (m/s), measured by the 10-meter walk test (10MWT), was the primary outcome measure and is predictive of community independence among PwMISCI (van Hedel & Group, 2009; van Silfhout et al., 2017). Participants completed three 10MWT trials over a 14-meter path with a 2-meter acceleration zone and were instructed to "*walk as quickly and safely as possible*" using their usual assistive devices for all walk trials. Types (counts) of devices used were as follows: rolling walker (n=10), crutches/canes (n=6), ankle-foot orthoses (n=3), Swedish knee cage (n=1). No more than contact guard assistance was provided during walk tests. Walking speed was analyzed using the mean value obtained from all walk trials at each time point.

Total walking distance (m), measured by the 2-minute walk test (2MWT), was collected as a secondary outcome measure. The use of the 2MWT rather than the 6-minute walk test allowed for the inclusion of individuals whose impairments might have limited their ability to walk for 6-minutes. During the 2MWT, participants were asked to "*cover as much distance as safely as possible*". Total distance walked was used in the analyses.

2.2.4.2 Gait quality

Gait quality was quantified by spatiotemporal gait characteristics (cadence [strides/min], stride length [cm] and step length [cm] of the weaker and stronger limbs) collected via instrumented walkway (GAITRite, CIR Systems Inc., NJ, USA). Step length asymmetries contribute to instability and walking dysfunction (Waters & Mulroy, 1999).

Step symmetry index (SI), previously characterized in persons with SCI (Nooijen et al., 2009), was calculated as:

$$SI = \frac{SLs - SLw}{0.5(SLs + SLw)} * 100\%$$

where *SLs*=step length (cm) of the stronger leg and *SLw*=step length (cm) of the weaker leg. Stronger/weaker legs were determined from baseline LEMS. Calculated SI was converted to absolute value (zero represented perfect symmetry). Spatiotemporal gait characteristics were analyzed using the mean value obtained from all walk trials at each time point.

2.2.5 Data analysis

Data were analyzed using SPSS v26 (IBM, 2019). Descriptive statistics, histograms, and Q-Q plots were examined for outliers and distributional abnormalities. Visual inspection and Shapiro Wilk's tests indicated normal distributions at each time point for the primary and secondary outcomes, apart from step symmetry index among both groups and walking speed among the MST+tDCS$_{sham}$ group (i.e., bimodal distribution at D1 and D5). We consulted 3 statisticians (2 within our organization and 1 outside the organization) and reviewed the existing literature (Hayat & Hedlin, 2012; Knief & Forstmeier, 2021; Lo & Andrews, 2015; Schielzeth et al., 2020) to ascertain the most appropriate statistical approach to be used. These efforts resulted in a decision to analyze the data using parametric statistics.

Main and interaction effects were analyzed using linear mixed-effects models. TIME, GROUP, and TIMExGROUP interaction were fixed effects. SUBJECT was

identified as a random factor using a 'random intercepts by participant' approach. Covariance structure was modelled using variance components, and model parameters were calculated using restricted maximum likelihood estimation (for small sample sizes) (Meteyard & Davies, 2020). Degrees of freedom estimation was performed using Satterthwaite approximation. Within-groups pairwise comparisons were examined using paired-samples t-tests. According to recommendations for the development of pilot studies in clinical research (Moore et al., 2011), α was set *a priori* at 0.10 in order to protect against the premature rejection of a potentially beneficial effect of the intervention.

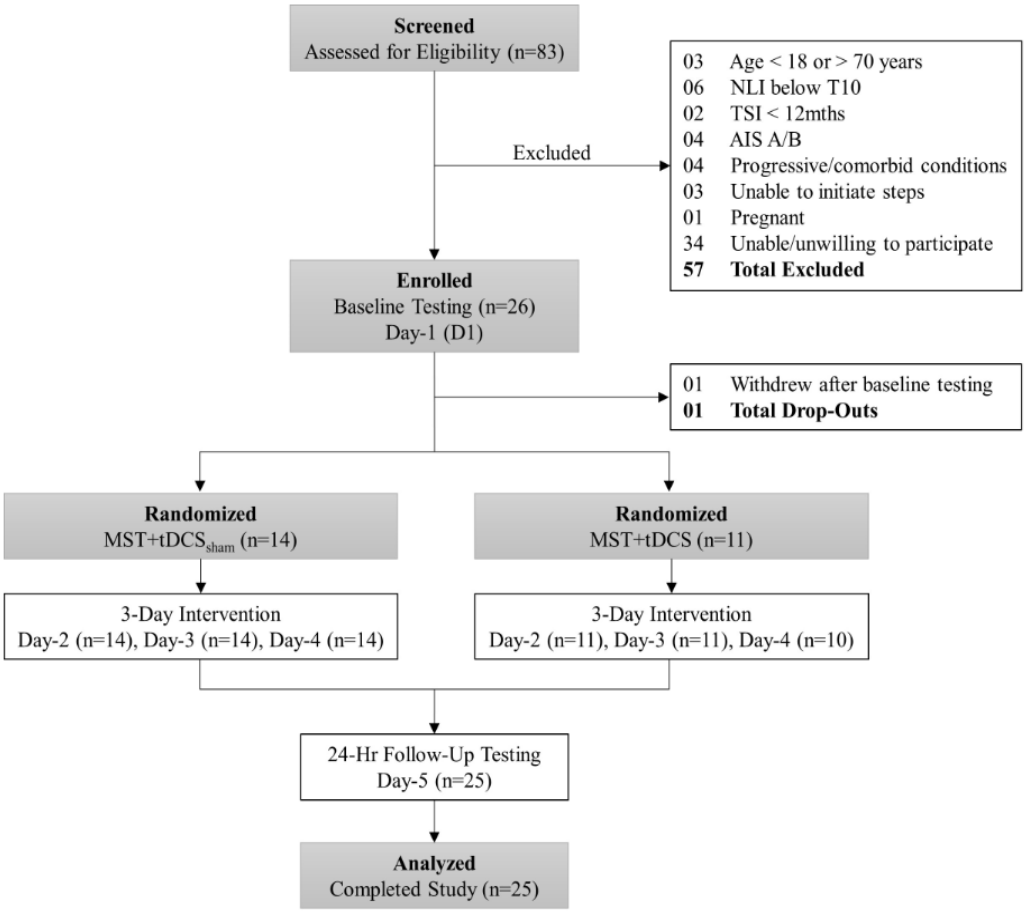


Figure 2.3. Recruitment and enrollment flow diagram. Abbreviations: NLI, *neurological level of injury*; TSI, *time since injury*; AIS, *ASIA Impairment Scale*.

Responsiveness of outcome measures to intervention was assessed via Hedges' g effect size for small sample sizes and correlated observations ($\text{Hedges's g} = Cohen's\ d \times \left[1 - \frac{3}{4(n_1+n_2)-9}\right]$) (Lakens, 2013). Meaningful differences for the 10MWT in PwMISCI have been variously reported as 0.06m/s (Musselman, 2007), 0.13m/s (Lam et al., 2008), and 0.15m/s (Forrest et al., 2014). We used the most conservative threshold to characterize a minimally clinically important difference (MCID) in walking speed (≥0.15m/s).(Forrest et al., 2014)

2.3 Results

2.3.1 Participants

Twenty-six participants with MISCI were recruited from the community and enrolled between *March, 2017* and *March, 2020*; one withdrew after baseline testing. Enrollment was terminated early due to COVID-19. Two protocol deviations were made (2 participants were enrolled 11-months post-injury due to their inability to participate in the study otherwise). Twenty-five participants were randomized to either MST+tDCS$_{sham}$ (n=14) or MST+tDCS (n=11) (Figure 2.3). Group characteristics at baseline are presented in Table 2.1 (statistical comparisons between baseline characteristics are reported in Appendix A.1). Eight adverse events (AEs) were reported during the study: 4 AEs associated with tDCS (12.5% of total sessions) including mild-to-moderate post-stimulation headache; 4 AEs associated with MST (0.05% of total sessions) including delayed-onset muscle soreness (n=2) and skin irritation (n=2). Six MST deviations were documented. Two participants were unable to complete activity #3 without upper extremity

support and were permitted to complete squats with hands on a fixed bar. Three participants were permitted to perform high velocity squats as opposed to explosive jumps (activity #4) due to muscle soreness and skin irritation experienced after the first intervention day. One participant completed only two days of intervention due to persistent headache on the third day.

Table 2.1. Baseline participant demographics and clinical characteristics.

Characteristics	**MST+tDCS$_{sham}$ (n=14)**	**MST+tDCS (n=11)**
Age (years)	46.7 ± 15.0 (19 - 63)	50.5 ± 10.7 (29 – 69)
Sex (male/female)	M=10 / F=4	M=8 / F=3
Time Since Injury (months)	93.2 ± 85.3 (12 – 236)	78.5 ± 93.0 (11 – 276)
Neurological Level of Injury	C3-C8=13 / T1-T10=1	C3-C8=09 / T1-T10=2
AIS Classification	C=1 / D=13	C=1 / D=10
ISNCSCI LEMS (total score)	37.1 ± 9.2 (22 – 49)	41.1 ± 8.3 (26 – 50)
10MWT Speed (m/s)	0.72 ± 0.53 (0.18 – 1.84)	0.64 ± 0.51 (0.07 – 1.77)
BMI (m/kg^2)	23.3 ± 4.6 (15.8 – 31.1)	26.0 ± 6.1 (19.3 – 39.6)
GXT VO_{2peak} (ml/kg/min)	17.5 ± 5.8 (10.3 – 27.5)	16.2 ± 5.0 (7.3 – 24.8)
GXT HR_{peak} (bpm)	134.2 ± 22.7 (107 – 180)	126.8 ± 20.5 (101 – 167)
Smoking Status	No=14 / Yes=0	No=8 / Yes=3
Medications	antispasmodics (10) analgesics (2) antihypertensive (1) antidepressive (1) neurogenic bowel/bladder (2) anti-inflammatory (1) anticoagulant (1) antipsychotic (1) none (3)	antispasmodics (9) analgesics (5) antihypertensive (1) antidepressive (7) neurogenic bowel/bladder (4) anti-inflammatory (2) anticoagulant (3) anti-anxiety (2) statins (1) none (1)

Note: Continuous variables reported as mean ± SD (min – max range). Categorical variables reported as counts. Medications indicate total number of participant reports. Abbreviations: AIS, *ASIA impairment scale*; ISNCSCI, *International Standards for Neurological Classification of Spinal Cord Injury*; LEMS, *lower extremity motor score*; BMI, *body mass index*; GXT, *graded exercise test*; VO_{2peak}, *peak oxygen consumption*; HR_{peak}, *peak heart rate*; bpm, *beats per min.*

Heart rate data during MST were collected for all but one participant (MST+tDCS$_{sham}$ group: We were unable to achieve consistent contact between the participant's skin and chest strap). MST duration and relative intensity was 37:19 mm:ss (SD=7:02) and 56.5% HRR (SD=14.0), respectively, for the MST+tDCS$_{sham}$ group and 37:12 mm:ss (SD=5:35) and 56.1% HRR (SD=8.6), respectively, for the MST+tDCS group. There were no between-groups differences in mean MST duration or intensity. The number of participants who achieved mean intensities of low (<40% HRR), moderate (40-60% HRR), and high (>60% HRR) across all intervention days was n=1, n=6, and n=6 within the MST+tDCS$_{sham}$ group and n=0, n=5, and n=6 within the MST+tDCS group. Group and individual HR_{avg} and %HRR data are presented in Figure 2.4.

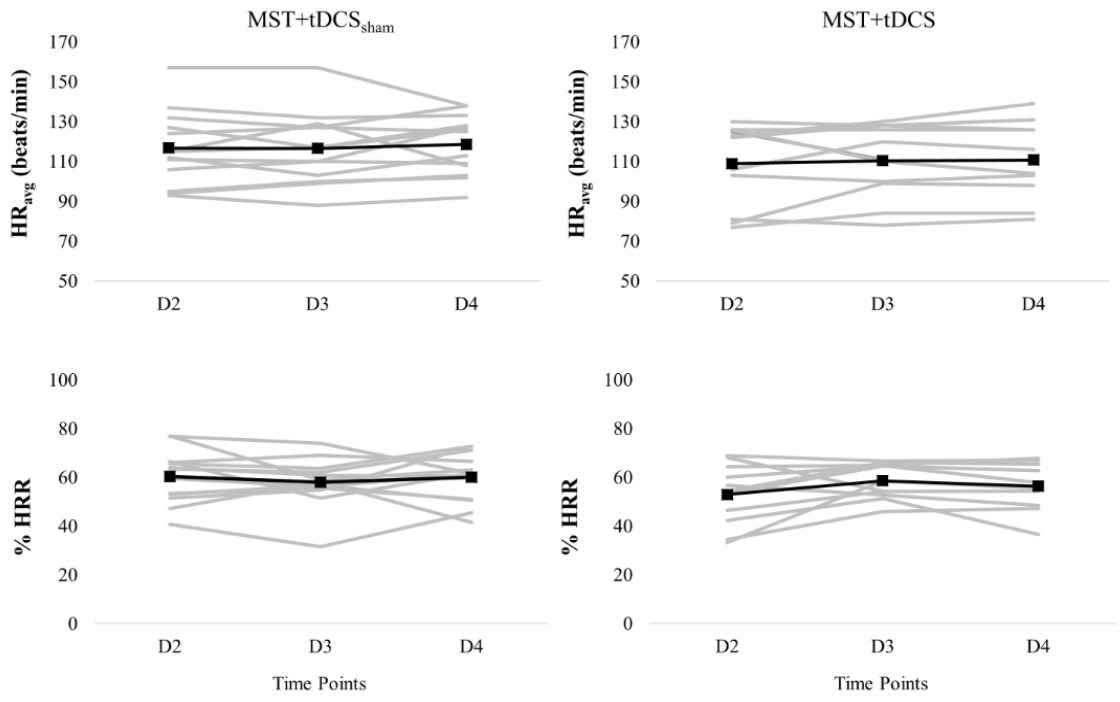


Figure 2.4. Group mean (black lines) and individual participant (grey lines) average heart rate (HR_{avg}) and % heart rate reserve (%HRR) collected over three consecutive days of intervention (Day-2 [D2], Day-3 [D3], Day-4 [D4]).

2.3.2 Walking function

2.3.2.1 Walking speed and distance

There was a significant effect of TIME on walking speed, $F(7,161)=11.69$, $p<0.001$. Neither GROUP nor TIMExGROUP interaction contributed to differences. Results of LMM analysis are reported in Appendix A.2. Within-group pairwise comparisons for the main effect of TIME showed a significant increase in walking speed within each group. From D1 to D5, the MST+tDCS$_{sham}$ group increased from 0.72 m/s (SD=0.53) to 0.85 m/s (SD=0.56; $t(13)=3.55$, $p<0.01$). The MST+tDCS group increased from 0.64 m/s (SD=0.51) to 0.77 m/s (SD=0.46; $t(10)=3.34$, $p<0.01$). Responsiveness of walking speed to intervention within the MST+tDCS group ($ES=0.97$) and the MST+tDCS$_{sham}$ group ($ES=0.92$) was large.

Change in walking speed within both the MST+tDCS and MST+tDCS$_{sham}$ groups ($\Delta M=0.13$ m/s, SD=0.13) approached, but did not reach the MCID of 0.15 m/s. While the percentage of participants that increased walking speed at D5 was greater among the MST+tDCS group (90.9%) compared to the MST+tDCS$_{sham}$ group (78.6%), the percentage of participants reaching the MCID was comparable between groups (36.4% and 42.9%, respectively) (Table 2.2).

There was a significant effect of TIME on walking distance, $F(1,23)=27.52$, $p<0.001$. Neither GROUP nor TIMExGROUP interaction contributed to differences. Results of LMM analysis are reported in Appendix A.3. Within-group pairwise comparisons showed a significant increase in walking distance within both groups. From D1 to D5, the MST+tDCS$_{sham}$ group increased from 83.1 m (SD=49.4) to 93.7 m (SD=50.3; $t(13)=4.91$, $p<0.001$). The MST+tDCS group increased from 77.1 m (SD=55.3) to 86.7 m (SD=50.7; $t(10)=2.85$, $p=0.02$). The percentage of participants who increased walking distance at D5 was comparable between the MST+tDCS group (81.8%) and the MST+tDCS$_{sham}$ group (85.7%). Walking distance decreased from D1 to D5 among 4 participants (2 per group). Paired comparisons of walking speed and walking distance are presented in Figure 2.5/Table 2.3.

Table 2.2. Count and percentage of participants who reached or did not reach the change threshold of 0.15 m/s considered as the minimally clinically important difference (MCID) in walking speed.

GROUP	NO CHANGE ($\Delta < 0.15$ m/s)		CHANGE ($\Delta \geq 0.15$ m/s)	
	Count	% Sample	Count	% Sample
MST+tDCS	7	63.6	4	36.4
MST+tDCS$_{sham}$	8	57.1	6	42.9
Full Sample	15	60.0	10	40.0

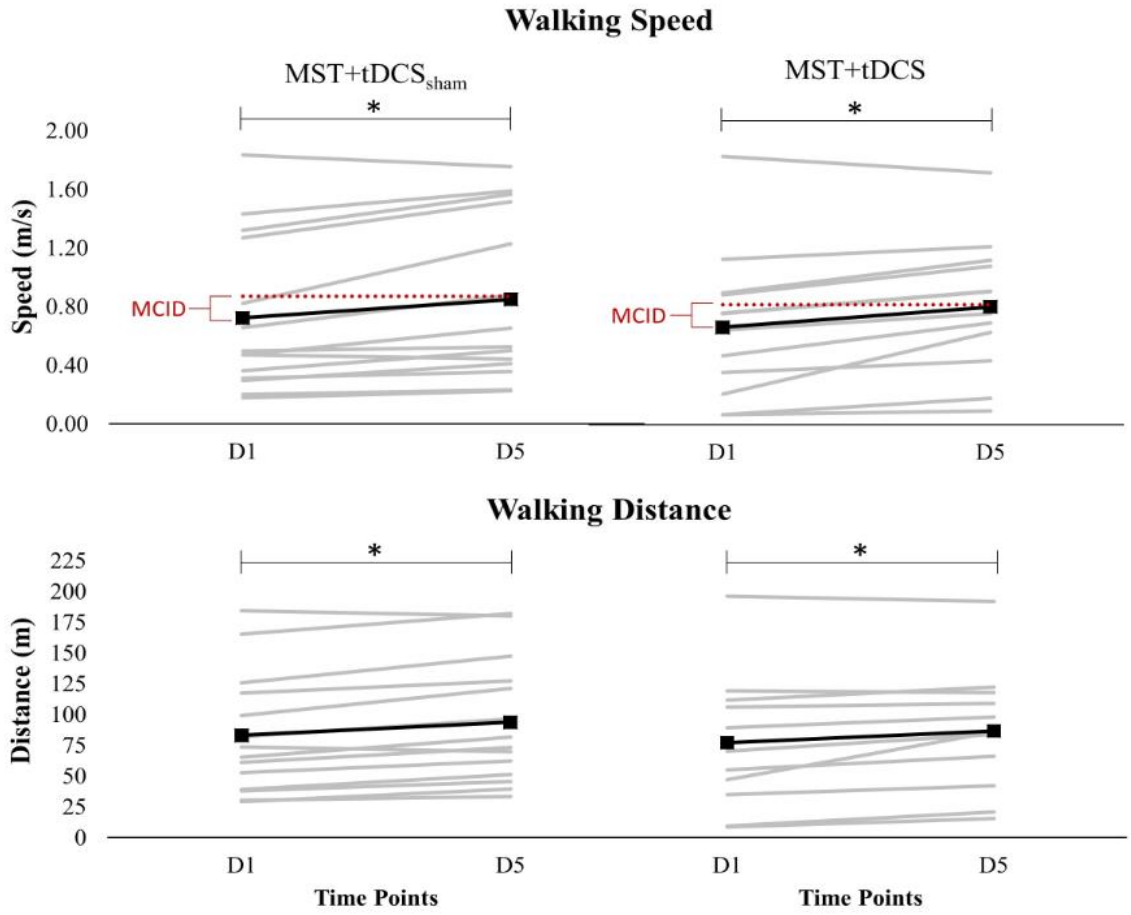


Figure 2.5. Group mean (black lines) and individual participant (grey lines) overground walking speed (m/s) and walking distance (m) at baseline Day-1 (D1) and 24-hours post-intervention Day-5 (D5) within the MST+tDCS$_{sham}$ and MST+tDCS groups. Red dotted line indicates the minimally clinically important difference (MCID) threshold of 0.15m/s (Forrest, et al., 2014). Group mean change in walking speed within the MST+tDCS$_{sham}$ and MST+tDCS groups = 0.13m/s. *Significant within-group difference (p<0.10).

Table 2.3. Mean (SD) and mean change (95% CI) for walking speed, walking distance, and spatiotemporal gait characteristics at baseline Day-1 (D1) and 24-hours post-intervention on Day-5 (D5) within the MST+tDCS$_{sham}$ and MST+tDCS groups and for the combined study sample.

	MST+tDCS$_{sham}$ (n=14)				**MST+tDCS (n=11)**				**Combined Sample (n=25)**			
Outcome	D1	D5	ΔD1-D5	Effect Size	D1	D5	ΔD1-D5	Effect Size	D1	D5	ΔD1-D5	Effect Size
Walking Speed (m/s)	0.72 (0.53)	0.85 (0.56)	**0.13*** (0.05, 0.20) $p = 0.004$	0.92	0.64 (0.51)	0.77 (0.46)	**0.13*** (0.04, 0.22) $p = 0.008$	0.97	0.69 (0.51)	0.82 (0.51)	**0.13*** (0.07, 0.18) $p < 0.001$	0.98
Walking Distance (m)	83.1 (49.4)	93.7 (50.3)	**10.5*** (5.9, 15.2) $p < 0.001$	0.20	77.1 (55.3)	86.7 (50.7)	**9.6*** (2.1, 17.1) $p = 0.017$	0.17	80.5 (51.1)	90.6 (49.5)	**10.1*** (6.3, 14.0) $p < 0.001$	0.19
Cadence (strides/min)	73.9 (34.3)	81.5 (34.9)	**7.6*** (3.2, 12.1) $p = 0.002$	0.97	70.7 (38.5)	82.1 (34.9)	**11.4*** (4.2, 18.5) $p = 0.005$	1.03	72.5 (35.5)	81.8 (34.2)	**9.3*** (5.5, 13.0) $p < 0.001$	1.00
SL-Weak (cm)	106.6 (33.5)	114.7 (35.6)	**8.1*** (4.1, 12.2) $p = 0.001$	1.14	95.0 (33.4)	104.5 (27.8)	**9.4*** (1.7, 17.2) $p = 0.022$	0.78	101.5 (33.3)	110.2 (32.2)	**8.7*** (5.0, 12.5) $p < 0.001$	0.94
SL-Strong (cm)	106.7 (33.1)	114.5 (35.5)	**7.8*** (3.2, 12.3) $p = 0.003$	0.95	94.4 (32.9)	103.7 (28.0)	**9.3*** (1.9, 16.7) $p = 0.018$	0.82	101.3 (32.9)	109.8 (32.2)	**8.4*** (4.6, 12.2) $p < 0.001$	0.90
Step Symmetry Index - SI (%)	14.6 (12.2)	16.2 (20.8)	1.7 (-4.9, 8.3) $p = 0.592$	0.14	12.3 (7.4)	13.6 (11.8)	1.3 (-2.6, 5.1) $p = 0.481$	0.21	13.6 (10.2)	15.1 (17.1)	1.5 (-2.3, 5.3) $p = 0.425$	0.16

Note: *p<0.10. Symmetry index (SI) value of zero indicates perfect symmetry. Effect size calculated using Hedges' g correction. Abbreviations: MST+tDCS$_{sham}$, *motor skill training + sham tDCS*; MST+tDCS, *motor skill training + active tDCS*; SL-Weak, *stride length of the weaker limb*; SL-Strong, *stride length of the stronger limb*.

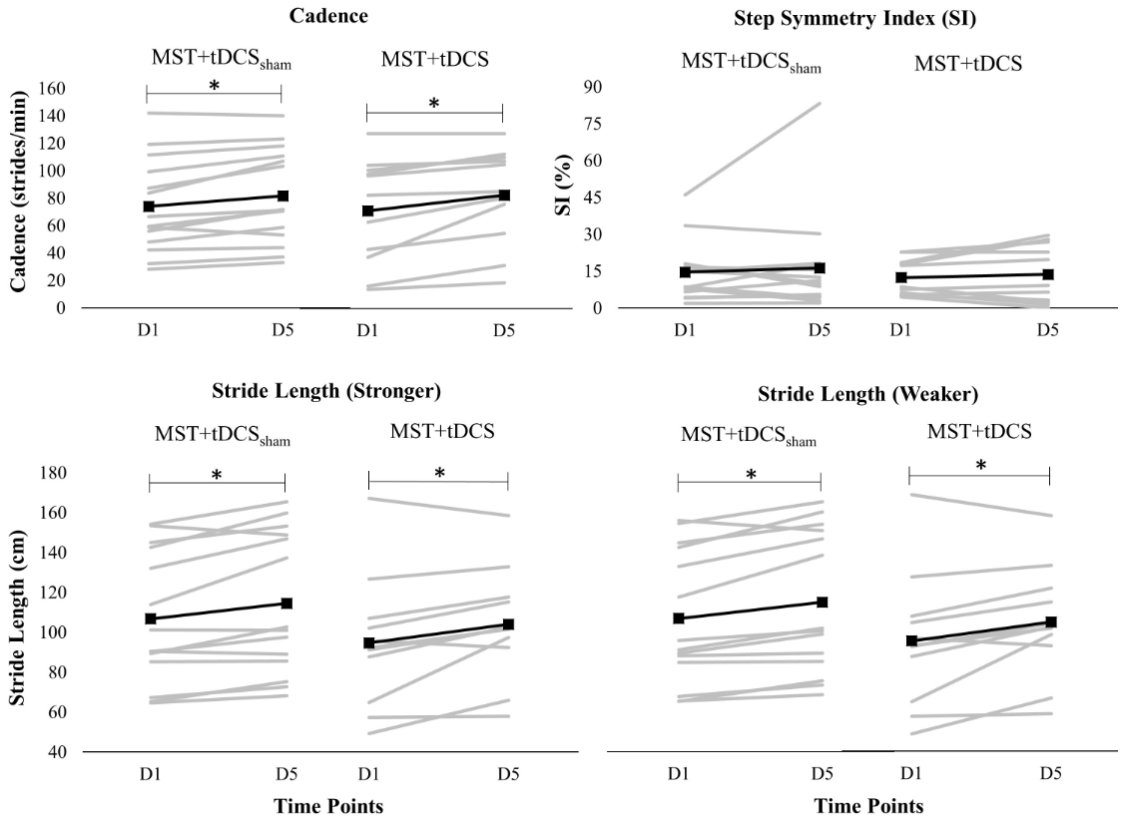


Figure 2.6. Group mean (black lines) and individual participant (grey lines) spatiotemporal gait characteristics, including cadence (strides/min), step symmetry index (absolute %), stride length of the weaker limb (cm), and stride length of the stronger limb (cm), obtained during the 10-Meter Walk Test at baseline Day-1 (D1) and 24-hours post-intervention Day-5 (D5). SI values closer to zero indicate greater interlimb step symmetry. *Significant within-group difference (p<0.10).

2.3.3 Gait quality

2.3.3.1 Spatiotemporal gait characteristics

There was a significant effect of TIME on cadence (F(7,160)=12.71, p<0.001), stronger limb stride length (F(7,160)=10.31, p<0.001), and weaker limb stride length (F(7,160)=9.73, p<0.001). There was no effect of GROUP or TIMExGROUP interaction on cadence (Appendix A.4) or stride length of the weaker (Appendix A.5) or stronger limb

(Appendix A.6). There were no effects of TIME, GROUP, or TIMExGROUP interaction on SI (Appendix A.7).

Within-group pairwise comparisons showed a significant increase in cadence from D1 to D5 for each group. The MST+tDCS$_{sham}$ group increased from 73.9 strides/min (SD=34.3) to 81.5 strides/min (SD=34.9); $t(13)=3.75$, $p<0.01$). The MST+tDCS group increased from 70.7 strides/min (SD=38.5) to 82.1 strides/min (SD=34.9; $t(10)=3.56$, $p<0.01$). Within the MST+tDCS$_{sham}$ group, stride length of the stronger and weaker limbs increased by 7.8 cm (SD=7.9; $t(13)=3.66$, $p<0.01$) and 8.1 cm (SD=7.0; $t(13)=4.37$, $p<0.01$), respectively. Within the MST+tDCS group, stride length of the stronger and weaker limbs increased by 9.3 cm (SD=11.0; $t(10)=2.81$, $p=0.02$) and 9.4 cm (SD=11.6; $t(10)=2.70$, $p=0.02$), respectively. Although no changes in SI were observed, SI values were greater than in non-disabled adults (Blazkiewicz et al., 2014; Kodesh et al., 2012), indicating greater asymmetry within our cohort. Paired comparisons of spatiotemporal gait characteristics are presented in Figure 2.6/Table 2.3.

2.4 Discussion

In participants with MISCI, a 3-day intensive locomotor-related MST program, with and without tDCS, was associated with significant increases in overground walking speed, walking distance, cadence, and bilateral stride length. The addition of tDCS was not associated with greater improvements compared to tDCS$_{sham}$. Although it is possible that failure to reach the target sample size contributed to an inability to detect between-groups differences in outcomes, it has been suggested that group-level sample sizes of 12

participants are sufficient to provide adequate measures of precision about the mean and variance in early intervention trials (Julious, 2005). Therefore, despite sample sizes being unbalanced between groups, the outcomes were strikingly similar such that even if statistically significant between-groups differences were to be identified with a much larger study, it seems unlikely that the differences would be consequential.

Although 0.13m/s change in walking speed failed to reach the MCID of 0.15 m/s, a distinctive finding of the present study was the magnitude of change observed despite the short intervention period. This change is comparable to observations in longer training studies. For example, five randomized clinical trials with training durations ranging from 6- to 24-weeks reported improvements in overground walking speed ranging from 0.01–0.16 m/s (Alexeeva et al., 2011; Field-Fote & Roach, 2011; Jones et al., 2014b; Kapadia et al., 2014; Lotter et al., 2020). Furthermore, improvement in walking speed among our sample was not limited to the 10-meter distance, as increases in the 2MWT were also observed, albeit the effect was small. The 10-meter and 2-minute walk tests are intended to assess distinct aspects of walking capacity (i.e., speed vs. endurance, respectively). Consequently, the effect of training on these measures may differ depending on the mode and duration of the approach employed. Additionally, responsiveness of outcomes to training may be dependent on the individual functional characteristics of participants in the study (Amatachaya et al., 2014). Differences in magnitude of effect of MST on walking speed and distance in the present study may be attributed to these factors. Nevertheless, measures of walking speed and distance improved 24-hours after the final session of the 3-day intervention, providing evidence for short-term persistent effects of training. Evidence indicates that training interventions that are challenging, promote exploration of motor

solutions, and provide the opportunity to make and correct errors are likely to be more effective for promoting motor learning and skill acquisition compared to interventions that do not provide these opportunities (Emken et al., 2007; Mutha et al., 2011). These were important considerations in the development of the MST circuit, which included locomotor-related activities involving cyclic and ballistic movements targeting motor deficits experienced by PwMISCI. These activities may be of value by offering a training approach that is comparable in effectiveness to locomotor training while overcoming issues of accessibility and cost of long-term participation. Feasibility studies would be needed to examine whether this training approach could be implemented safely and effectively in the home or community.

In the present study, we emphasized maintaining physiological intensities of at least moderate-intensity based on %HRR (i.e., 40-60% HRR). Our data confirmed that, on average, the cardiovascular demands of participation met this objective (i.e., mean %HRR=56%); however, one participant in our study failed to reach the intended target. Evidence highlights the importance of training intensity as a means of influencing neuroplasticity for improved motor function in persons with neurologic conditions (Leech & Hornby, 2017; Mang et al., 2016; Rojas Vega et al., 2008). Moderate- to high-intensity motor training appears to be superior to low-intensity training in this respect (Brazg et al., 2017; Fisher et al., 2008; Hasan et al., 2016; Leech et al., 2016). Hypothesized mechanisms include enhanced blood flow to brain regions involved in motor control and learning (Singh & Staines, 2015), upregulation of glucocorticoids (Milani et al., 2010) and neurotrophic factors (He et al., 2013), and increased arousal (McMorris et al., 2015). While a recent pilot study in PwMISCI intended to compare high- versus low-intensity training based on

percent estimated maximum heart rate, the majority of participants failed to achieve target cardiovascular thresholds during locomotor training (Brazg et al., 2017). Autonomic nervous system dysfunction and cardiorespiratory dysregulation are well-documented in SCI (West et al., 2013), especially for those with injuries at or above the neurological level of T6, making objective and reliable quantification of physiological intensity difficult during exercise. Given this challenge, complimentary approaches to quantifying exercise intensity, such as measures of blood lactate or volume of oxygen consumed, may be needed to disentangle the relationship between physiological intensity of motor training and functional outcomes. This consideration would strengthen the interpretability of future studies that purport to capitalize on physiological mechanisms subserving the neuromodulatory benefits of higher intensity training.

Although several studies have reported a favorable influence of combined tDCS and motor training on upper extremity function in PwMISCI (Cortes et al., 2017; Gomes-Osman & Field-Fote, 2015a; Potter-Baker et al., 2018; Yozbatiran et al., 2016), the effects on lower extremity function are equivocal. Two small studies have examined tDCS combined with robotic-assisted treadmill training (Kumru et al., 2016; Raithatha et al., 2016). Our findings are consistent with these previous reports in that changes in walking function did not differ between tDCS and $tDCS_{sham}$ groups. In one study, it was suggested that injury severity contributed to lack of effect of tDCS (Kumru et al., 2016); however, despite greater motor function in our cohort, we also failed to observe an effect. In neurologically intact adults, individual corticomotor responses to tDCS are highly variable (Horvath et al., 2016). This inherent variability, combined with the heterogeneity in functional presentation observed among PwMISCI (Dvorak et al., 2014), may complicate

group-level analyses of potential additive effects of tDCS. Future examinations of efficacy of this combined approach may be aided by identifying individual responders and non-responders to tDCS prior to intervention.

Our findings indicated that beyond walking speed and distance, significant increases in cadence and bilateral stride length were associated with the MST intervention. Changes were equivalent to those of a 12-week stratified, randomized study comparing four training approaches, wherein both cadence and bilateral stride length increased with all approaches (Nooijen et al., 2009). Likewise, in a case series report, 12-weeks of lower extremity resistance and ballistic training was associated with increases in bilateral step length (Gregory et al., 2007). Cadence and stride length are coupled to walking speed (Pepin et al., 2003; van Hedel et al., 2006). As such, changes in one or both of these spatiotemporal gait characteristics are anticipated and may shed light on processes underlying change in walking speed. For instance, SCI is associated with a reduced capacity to produce high stride frequencies of the lower limbs (Pepin et al., 2003). Consequently, inability to increase cadence limits walking speed after SCI (Pepin et al., 2003). Motor training interventions that emphasize cyclic, rapid volitional movements may be advantageous for increasing cadence and achieving faster walking speeds. Despite the positive findings related to walking function, cadence, and stride length, our participants had greater step length asymmetry compared to non-injured adults (Blazkiewicz et al., 2014; Kodesh et al., 2012) that was not improved with the MST intervention. Prior studies in PwMISCI have observed improvements in SI (Nooijen et al., 2009). Our sample was relatively high functioning and, with the exception of one outlier within the MST+tDCS$_{sham}$

group, did not exhibit the extent of step asymmetry at baseline that has been observed in prior studies. For this reason, there may have been a ceiling effect related to this measure.

A reasonable critique of the proposed MST circuit is that participation may be limited to those with greater levels of motor function. Mean baseline walking speed of our sample was relatively high for PwMISCI (i.e., M=0.69 m/s); however, a closer examination of individual participant characteristics and responsiveness to MST reveals some relevant observations worth noting. For instance, 36% (9 of 25) of participants enrolled in the study presented with baseline walking speeds <0.44 m/s, which is indicative of individuals who are wheelchair-dependent for community mobility (van Hedel & Group, 2009). Of those 9 participants, all completed the intervention, with modification provided as needed (see Methods). Further, all realized improvements in walking speed and distance. While findings from any pilot study should be interpreted with caution, these preliminary observations are sufficient grounds for the development of a larger study, with specific emphasis on conducting a thorough examination of the individual clinical characteristics that may predict responsiveness to the MST intervention.

2.4.1 Study limitations

Mean baseline walking speed and total LEMS differed between groups and were higher than some prior studies. Existing evidence from individuals with SCI indicates that lower extremity strength is associated with walking speed (DiPiro et al., 2015), and baseline walking speed may be a predictor of responsiveness to training (Jones et al., 2014a). In addition, our recruitment goal was not reached, perhaps leaving the study

underpowered to detect between-group differences. It is possible that we failed to detect an additive effect of tDCS when in fact an effect was present; however, this seems unlikely given the close similarity in outcomes between groups. The effectiveness of participant blinding to real vs sham tDCS was not assessed, and various electrode montages have been proposed for differentially modulating the neurophysiology of targeted structures. The reported findings should be viewed within the context of the specific tDCS electrode montage used. The absence of a non-MST control group makes it difficult to discern the unique contributions of the MST intervention, where the psychological influence of participant expectation on study outcomes cannot be ruled out given that all individuals received MST. The inclusion of an alternative exercise comparison group would strengthen future studies. Finally, while there were no differences in training duration between participants, it is possible that individuals with greater motor function completed more repetitions during MST. Tracking this training parameter over the course of a longer trial could reveal inter-individual differences that are consequential to observed outcomes.

2.5 Conclusions

Critical considerations of ongoing interest are the long-term accessibility and costs associated with obtaining meaningful improvements in walking function following SCI. The MST circuit was developed based on motor learning principles relevant to transferability of training effects, physiologic evidence for the value of intensive training to activate neuroplastic mechanisms, and the evidence for increasing corticospinal drive to influence motor outcomes. While no effect of tDCS was identified, the cyclic and ballistic

training activities appear to promote improvements in walking speed, distance, cadence, and stride length. Accounting for identified limitations, larger studies with longer training periods are warranted.

CHAPTER 3. WALKING AND BALANCE OUTCOMES ARE IMPROVED FOLLOWING BRIEF INTENSIVE LOCOMOTOR SKILL TRAINING BUT ARE NOT AUGMENTED BY TDCS IN PERSONS WITH CHRONIC SPINAL CORD INJURY

3.1 Introduction

Recovery of motor function, including walking and balance, is central to rehabilitation for persons with motor-incomplete spinal cord injury (PwMISCI). Given the functional and health-related value of standing and walking (Olson et al., 2018), even small improvements in locomotor function can have a significant impact on the long-term health, quality of life, and community re-integration of people living with MISCI (Gasper et al., 2019; Hiremath et al., 2017; McMillan et al., 2021). Because resources often limit the amount of time that individuals with SCI have access to rehabilitation services, therapies that extract the greatest benefit in the least amount of time are of ongoing interest. Further, because ongoing practice is important for maintaining gains acquired during rehabilitation, there is value in examining training approaches that could feasibly be carried out with supervision in the home or a community setting once individuals are discharged from traditional rehabilitation.

The restoration of motor function after neurological injury is dependent on the extent to which motor learning (i.e., the acquisition and long-term retention of new or previously learned motor skills) can be optimized. Frameworks for conceptualizing motor skill acquisition and retention have been described extensively (Higgins, 1991; Schmidt, 1975).

Existing evidence indicates that training-induced motor learning is achieved through a combination of online (within-day) and offline (between-day) processes (Dayan & Cohen, 2011; Reis et al., 2009; Robertson et al., 2004). The mechanisms underlying performance improvements observed within minutes to hours of a single training session (online learning) are different from those observed in the day(s) between training sessions (offline learning) (El-Sayes et al., 2019; Wanner et al., 2020). Various interventions have been deployed with the aim of specifically targeting mechanisms that support motor skill acquisition and retention. Intensive exercise (Singh, Duncan, et al., 2014; Skriver et al., 2014) and non-invasive brain stimulation (Gomes-Osman & Field-Fote, 2015a; Nitsche, Schauenburg, et al., 2003) have been explored as viable neuromodulation approaches that have the capacity to reinforce mechanisms that subserve neuroplasticity and motor learning through both online and offline processes.

Recent findings emphasize the importance of training *intensity* as a means of improving motor function and influencing neuroplasticity in persons with neuropathology (Fisher et al., 2008; Holleran et al., 2018; Leech et al., 2016; Mang et al., 2013). Of particular interest is the intensity-dependent release of brain-derived neurotrophic factor (BDNF), which facilitates and supports neuroplastic events within the nervous system (Cobianchi et al., 2017; Dinoff et al., 2016; Guo et al., 2014; Guo et al., 2018; Inoue et al., 2018; Mang et al., 2014; McDonnell et al., 2013; Phillips et al., 2014; Skriver et al., 2014; Yoshi & Constantine-Paton, 2009). Exogenous delivery of BDNF is associated with synaptic strengthening, neuronal sprouting, and improved locomotor recovery in pre-clinical models of SCI (Jakeman et al., 1998). Moderate- to high-intensity exercise is associated with increased endogenous levels of BDNF in individuals with SCI (Leech &

Hornby, 2017; Rojas Vega et al., 2008). In neurologically intact adults, a single session of intense cycling is associated with an increase in serum BDNF (Skriver et al., 2014) and enhanced motor cortical activity (Holman & Staines, 2021), which, in both cases, were positively correlated with retention of a novel motor task. It is believed that higher-intensity motor training is superior to lower-intensity training for improving motor function through the upregulation and release of BDNF that encourages mechanisms that support skill acquisition and learning.

Transcranial direct current stimulation (tDCS) is increasingly used in rehabilitation research as a neuromodulatory approach to influence excitability of cortical (Nitsche & Paulus, 2000) and cerebellar (Celnik, 2015) networks. Most often, the aim is to "prime" neural circuits to increase corticospinal activation and to augment effects of motor skill training (Page et al., 2015; Sriraman et al., 2014). Evidence in non-injured adults indicates that concurrent application of anodal-tDCS over the primary motor cortex with motor skill training enhances learning by facilitating offline mechanisms that support motor program consolidation (Kim, Kim, et al., 2021; Reis et al., 2009). Furthermore, cathodal-tDCS over the cerebellum reduces the inhibitory influence of the cerebellum on thalamo-cortical structures involved in motor control (Galea et al., 2009) and is associated with improved locomotor and balance function in persons with neuropathology (Kaski et al., 2013).

Several prior studies by our lab and others have investigated tDCS for augmenting upper extremity training in persons with tetraplegia (Cortes et al., 2017; Estes et al., 2017; Gomes-Osman & Field-Fote, 2015a; Potter-Baker et al., 2018; Yozbatiran et al., 2016). Very little is known about the influence of combining tDCS with motor training to improve lower extremity motor function in PwMISCI. To date, only two studies have examined this

combinatorial intervention approach for improving locomotor and balance function. Both involved the application of tDCS along with robotic-assisted treadmill training (Kumru et al., 2016; Raithatha et al., 2016), which is a locomotor training approach that often lacks intensity and is rarely accessible to PwMISCI once discharged to the home. Moreover, neither study examined the acute temporal influence (i.e., within- and between-day responses) associated with these combined interventions. Characterizing online versus offline training effects in PwMISCI will be valuable for future studies aimed at exploring the potential mechanisms underlying motor learning following combined motor training and tDCS.

In light of the above, locomotor skill training that capitalizes on the neuroplastic effects of intensive exercise and can be implemented in the home or community may have potential for meaningful impact on the long-term restoration and retention of walking and balance function. Additionally, training effects may be augmented by tDCS by influencing mechanisms that support motor skill acquisition and consolidation. Previously, we reported significant persistent effects of 3 days of intensive locomotor skill training on measures of walking ability (Evans & Field-Fote, 2022). The purpose of this study was to examine the within-day and between-day effects of three consecutive days of moderate-intensity motor skill training (MST), with and without tDCS, on measures of walking and balance function in persons with MISCI. We hypothesized that MST would be associated with improvements in walking and balance function and that the addition of tDCS would lead to greater improvements than MST alone.

3.2 Materials and Methods

3.2.1 Study design

This pilot study was conducted as a multi-session double-blind, randomized intervention (ClinicalTrials.gov Identifier: NCT03237234). Participants were randomly assigned to one of two groups ([1] MST with concurrent sham tDCS [MST+$tDCS_{sham}$] or [2] MST with concurrent active tDCS [MST+tDCS]) using the REDCap randomization module. Participants, trainers, and assessors were blinded to tDCS group allocation. The tDCS was applied by a staff member not otherwise involved in the study. The study was carried-out over five consecutive days (Monday-Friday), with three intervention days (Tuesday–Thursday). The 3-day intervention was selected to establish preliminary evidence of efficacy prior to undertaking a longer study. Outcomes were assessed at baseline on Day-1 (D1) and 24-hours post-intervention on Day-5 (D5) to examine cumulative and persistent effects of intervention. To examine within- and between-day effects of intervention on outcome measures associated with walking, a subset of selected outcomes were assessed pre- ($D2_{pre}$, $D3_{pre}$, $D4_{pre}$) and post-intervention ($D2_{post}$, $D3_{post}$, $D4_{post}$) on each intervention day (Figure 3.1).

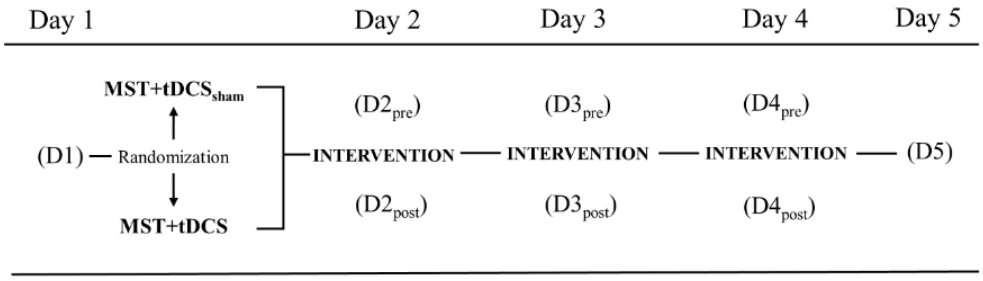


Figure 3.1. Study design with outcomes collected at baseline Day-1 (D1), pre-/post-intervention on Day-2 (D2), Day-3 (D3), Day-4 (D4), and 24-hours post-intervention on Day-5 (D5). Abbreviations: MST+$tDCS_{sham}$, *motor skill training plus sham transcranial direct current stimulation*; MST+tDCS, *motor skill training plus active transcranial direct current stimulation*.

3.2.2 Study sample

The sample size was calculated on the basis of change in the primary outcome measure (overground walking speed) previously reported in participants with MISCI, wherein an effect size of 0.69 was identified (Manella et al., 2013). To achieve a power=0.80 at α=0.10 (one-sided), a sample size of 15 participants per group was calculated (G*Power 3.1: F tests, ANOVA repeated measures, between-factors). Inclusion criteria were: (a) chronic MISCI (≥12 months) at/above the neurological level T10, (b) aged 18-70 years, (c) able to stand for ≥5 minutes, and (d) able to advance each leg independently ≥3 steps. Exclusion criteria were: (a) progressive spinal lesions, (b) uncontrolled cardiorespiratory conditions, (c) altered cognitive status, (d) orthopedic pathology, (e) intracranial metal, and (f) history of seizures. Injury characteristics (i.e., ASIA Impairment Scale [AIS] classification and lower extremity motor scores [LEMS]) were obtained at the time of enrollment from participant medical records (if completed within the prior 6-months) or following neurological examination by a member of the research team.

3.2.3 Interventions

3.2.3.1 Motor skill training (MST)

Details of the MST intervention have been described previously (Evans & Field-Fote, 2022). Briefly, six activities were selected that could feasibly be performed (with supervision) in the home or a wellness setting, with the aim of targeting muscle groups and movement patterns important to walking ability in persons with SCI (Crozier et al., 1992;

C. Kim et al., 2004; van Middendorp et al., 2011; Wirth et al., 2008a). Each motor task was performed for 60 seconds in consecutive order and repeated 4 times as a circuit (Figure 3.2). Participants were asked to complete as many repetitions as possible in the time allotted for each activity. The MST activities were intended to challenge upright standing balance and promote rapid volitional activation and deactivation of lower extremity muscles (i.e., hip, knee, and ankle extensors/flexors) through movements characterized by cyclic (Vietnen & Welch, 2020) and/or ballistic (Cordner et al., 2021) sequences. One seated activity was included in the circuit to provide an opportunity for active rest. For participants with greater motor impairment, modifications that did not substantively alter the intent of the activity were provided to ensure that all participants could complete each task. Examples included: providing a fixed bar for upper extremity support in cases where balance deficits made completing an activity unsafe or impossible (e.g., attempting a ballistic jump during activity #4); and providing manual assistance in cases where participants lacked sufficient strength to achieve the range of motion needed to accomplish the goal of the task (e.g., lifting the foot to the step during activity #2).

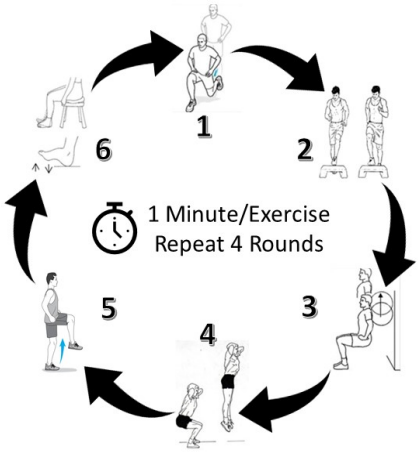


Figure 3.2. Locomotor-related motor skill training (MST) circuit. Six exercises were performed for one minute each, and the circuit was completed four times. Target MST intensity was 40-59% of heart rate reserve. Images of a representative participant completing the circuit can be found in Figure 2.1.

Training intensity was monitored continuously throughout the MST circuit and quantified via heart rate obtained using a chest-worn monitor and wristwatch (Polar FT1; Polar Electro Inc., Woodbury, NY, USA). Average (HR_{avg}) and peak (HR_{peak}) heart rate were recorded for each session. During MST, participants were encouraged to perform the activities as rapidly as possible with the intent to maintain a moderate exercise intensity, recognized as 40-60% heart rate reserve (HRR). Ranges for %HRR were established for each participant according to resting heart rate and HR_{peak} obtained from baseline maximal graded exercise testing performed via upper body cycle ergometer (Monark 881E Arm Ergometer; Monark Exercise AB, Vansbro, Sweden). Graded exercise testing procedures followed accepted practices (*ACSM's Guidelines for Exercise Testing and Prescription*, 2018).

3.2.3.2 Transcranial direct current stimulation (tDCS)

TDCS (ActivaDose II; Activa Tek Inc., Gilroy, CA, USA) was delivered via two 5x5cm electrodes (0.9% saline-soaked sponges): the anode was placed slightly anterior to the vertex over bilateral primary motor cortices, and the cathode was placed at the inion over the cerebellum. This electrode montage was chosen based on previous reports for modulation of brain regions involved in lower extremity motor control (Kaski et al., 2013; Kaski et al., 2012; Mang et al., 2016). Electrodes were secured using elastic straps that had been marked to replicate placement location. For participants in the active tDCS condition, 20-minutes of stimulation was delivered concurrently with MST at an intensity of 2mA (current density = 0.80 A/m^2; charge density = 0.96 kC/m^2). For participants receiving sham tDCS, set-up procedures were identical to the active tDCS condition; however, a

ramp-up/ramp-down sequence was employed wherein stimulation was gradually increased to 2mA and then decreased to 0mA over approximately 40-secs at the start of each MST session. Study personnel involved in administering tDCS were not involved in any other aspect of the study, and those involved in MST delivery and data collection were blinded to the stimulation condition.

3.2.4 Outcome measures

3.2.4.1 Walking Measures

The primary outcome measure of walking ability was overground walking speed (m/s), which is a common clinical measure and is predictive of community independence among persons with SCI (van Hedel & Group, 2009; van Silfhout et al., 2017). Measures of walking speed were obtained during the 10-meter walk test (10MWT). At each time point, participants completed three, 10MWT trials over a 14-meter path with 2-meter acceleration and deceleration zones located at the beginning and end of the path. Walk trials were separated by 2-minutes of seated rest. Instructions provided prior to each walk were to "*walk as quickly and as safely as possible*". Participants were permitted to use their usual assistive devices, which included rolling walkers (n=10), crutches/canes (n=6), ankle-foot orthoses (n=3), and a Swedish knee cage (n=1). Assistive walking devices were kept consistent between all walk trials. Mean walking speed of the three walk trials at each time point was used in the analysis.

Secondary outcome measures of walking ability included kinematic measures of gait quality. Kinematic data were obtained during each 10MWT using a 3D inertial measurement unit (IMU) motion capture system (Xsens MVN Biomech Awinda; Xsens

Technologies BV, Enschede, NL) and a 7-meter long instrumented walkway (GAITRite; CIR Systems Inc., Sparta, NJ, USA). Body dimensions were measured, and IMU sensors were affixed by elastic straps to the head, sternum, and pelvis, and bilaterally to the hands, forearms, upper arms, shoulders, thighs, shanks, and feet in accordance with manufacturer's specifications. IMU calibration was performed with participants standing in neutral pose (Npose; with arms by their sides and without the use of an assistive device). Kinematic data were sampled at 60hz for each walk trial. A customized computer code was developed in MATLAB (version R2021a; The MathWorks Inc., Natick, MA, USA) to extract relevant kinematic data generated by the IMU system (version 2019.0.0; Xsens MVN, Enschede, NL).

Stride frequency (i.e., cadence) and stride length are coupled to walking speed modulation in persons with SCI (Pepin et al., 2003) and therefore, were considered outcomes of interest. Stride frequency (strides/min) and stride length (cm) of the stronger and weaker lower limbs were extracted for each walk trial from full steps registered along the length of the instrumented walkway. Data from partial steps acquired at the beginning and the end of the instrumented walkway were excluded, and the average value across the three walk trials was used in the analysis. Outcomes extracted from IMU data included the peak trailing limb angle (TLA [°]) and the angular component of the coefficient of correspondence (ACC). Propulsive force is diminished in persons with SCI and is associated with a reduction in overground walking speed (Peters et al., 2018). Sixty-five percent of the increase in propulsive force generated during walking speed modulation can be attributed to increases in the TLA (Hsiao et al., 2015). Peak TLA has been characterized and validated as a surrogate measure of propulsive force in healthy adults (Hsiao et al.,

2015) as well as in persons with stroke (Lewek & Sawicki, 2019). We examined the extent to which the TLA of the stronger and weaker limbs was amenable to intervention. MATLAB output for TLA quantification was validated against TLA data obtained from a non-injured test participant using a 3D optical motion capture system (Vicon Motion Systems Ltd, UK) previously used to quantify the TLA (Miyazaki et al., 2019). Briefly, the positions of anatomical landmarks in the global frame were determined beginning at the pelvis and moving distally to the lower extremities and feet using a link segment (kinematic chain) model. For both the left and right lower extremities, TLA was calculated from sagittal plane kinematics according to the angle created by the vertical line passing through the hip and ankle joint during IMU calibration and the line connecting the location of the hip and ankle joint during each stride (see Appendix B.1) (Miyazaki et al., 2019). TLA values obtained during the acceleration and deceleration periods of each walk trial were excluded by calculating peak TLA from the average value obtained during the middle 50% of strides. Representative TLA data extracted from the IMU system during a single walk trial is provided in Appendix B.2. The average peak TLA (for each lower limb) from all walk trials at each time point was used in the analysis.

Intralimb coordination of the weaker and stronger limbs was calculated according to the angular component of the coefficient of correspondence (ACC) based on methods previously developed by members of our team. The ACC indicates the degree of stride cycle-to-cycle variability in hip-knee relative motion plots. Prior investigations have used this approach to examine intralimb coordination as a measure of the integrated function of motor systems involved in cyclic locomotor behavior in persons with SCI (Awai & Curt, 2014; Field-Fote & Tepavac, 2002; Tepavac & Field-Fote, 2001). In keeping with these

reports, we quantified the consistency of cycle-to-cycle kinematics of the hip and knee joints. Similar to TLA calculations, a single ACC value for each lower limb was computed from the middle 50% of strides for each walk trial, and the average ACC of three walks at each time point was used in the analysis. An ACC value of "1" indicates perfect cycle-to-cycle hip-knee angle consistency and a value of "0" indicates no cycle-to-cycle consistency. Stronger and weaker limbs identified for stride length, TLA, and ACC were determined from lower extremity motor scores obtained from manual muscle tests at baseline (D1). All walking measures were collected at all time points over the course of the study.

3.2.4.2 Balance Function

Balance performance and mobility confidence were assessed at baseline and at 24-hour post-intervention using the Berg Balance Scale (BBS) (Lemay & Nadeau, 2010) and the Falls Efficacy Scale-International (FES-I) (Dewan & MacDermid, 2014), respectively. The BBS contains 14 functional test items with each item scored on a 0-4 scale, with "0" indicating the lowest level of function and "4" indicating the highest level of function. Higher scores on the BBS indicate better balance performance. In individuals with SCI, concern for falling limits individual performance during overground motor tasks irrespective of functional ability to perform the task (John et al., 2010) and may influence balance performance. Fear of falling was assessed using the FES-I 16-item questionnaire. Each question addresses the participant's concern for falling during specific activities of daily living. Participants were asked to rate their concern for falling on each item using a four-point scale, where "1" indicates "*Not at all concerned*" and "4" indicates "*Very*

concerned". Higher scores on the FES-I indicate a greater fear of falling. To minimize participant burden, the BBS and the FES-I were only performed at baseline (D1) and 24-hours post-intervention (D5). Total scores for both measures were used in the analysis.

3.2.5 Data analysis

Data were managed in Microsoft Excel and analyzed using SPSS v27 (IBM, 2019). Outcomes were examined for outliers and distributional abnormalities. One participant in the MST+tDCS group did not complete $D4_{post}$ testing. In this case, mean replacement for the $D4_{post}$ time point was used based on the average of the previous two post-intervention time points. Mean group-level and full sample training characteristics (i.e., total training duration, training intensity) were calculated by first recording the mean total time and %HRR for each participant at each time point and then taking the average of these values across all intervention days (i.e., [D2 mean value + D3 mean value + D4 mean value]/3). The effects of intervention on walking speed, cadence, stride length, TLA, BBS, and FES-I were examined using a linear mixed-effects model with TIME, GROUP, and TIMExGROUP interaction treated as fixed effects. SUBJECT was identified as a random factor using a 'random intercepts by participant' approach. Covariance structure was modelled using variance components, with α set *a priori* at 0.10. An alpha of 0.10 was selected based on recommendations for designing and implementing pilot studies in clinical research (Moore et al., 2011), where higher levels of type I error rates (e.g., 10-25%) are accepted in order to screen for potential efficacious treatments and to avoid falsely rejecting interventions that may be beneficial. Model parameters were calculated

using restricted maximum likelihood estimation (for small sample sizes) (Meteyard & Davies, 2020). Degrees of freedom estimation was performed using Satterthwaite approximation. Given that participants completed multiple walk trials at each time point and to rule out the possible influence of walking speed variance on outcomes, we calculated the SD of the 3 walking speeds obtained from each participant at each time point. Linear mixed-effects model analysis revealed no differences in walk speed variance across TIME, $F(7/182)=1.16$, $p=0.327$), or between GROUPs, $F(1/182)=3.21$, $p=0.075$.

In the presence of significant findings for the primary and secondary outcome measures, post hoc pairwise comparisons examining differences in outcomes between time points were performed using paired-samples t-tests. In keeping with concern for falsely rejecting possible beneficial treatments, and given the small sample size of our study, we followed recommendations for developing exploratory and early phase studies (Feise, 2002; Parker & Weir, 2020) in which adjustment for multiple comparisons are not advised in order to decrease the chance of committing type II errors and to overcome the need to increase the sample size, which was not possible due to early termination of the study due to COVID-19 restrictions.

To examine within-day and between-day responses to intervention, cumulative change in outcomes for all within-day and between-day time points were calculated and between-groups and full sample differences were compared using independent samples t-test and paired samples t-test, respectively. ACC data for the stronger and weaker limbs were negatively skewed with significant Shapiro-Wilk's tests ($p<0.05$) at all time points; therefore, ACC data were analyzed using nonparametric tests. Differences within stronger and weaker limb ACC over TIME were analyzed using the Friedman test. GROUP

differences in change for the stronger and weaker limb ACC were examined using the Mann-Whitney U test. Post hoc comparisons of differences between time points were examined using a Wilcoxon signed-rank test. Descriptive statistics for parametric analyses are reported as mean (SD) and for nonparametric tests are reported as median (IQR). Responsiveness of the primary outcome (overground walking speed) to intervention was assessed via *Cohen's* d_z (Lakens, 2013) according to criteria established for effect size (*ES*) interpretation in multicomponent rehabilitation interventions (Kinney et al., 2020), where *ES* was considered small (d=0.14), medium (d=0.31), or large (d=0.55) .

3.3 Results

3.3.1 Participants

Twenty-six participants with chronic, MISCI were enrolled in the study between *March, 2017* to *March, 2020*, with one withdrawal after baseline testing. The intended sample size of 30 participants (15/group) was not reached due to early termination of enrollment. Two protocol deviations (2 participants enrolled at 11-months post-injury) were considered necessary to maximize our recruitment targets. Randomization resulted in 14 participants allocated to the MST+tDCS$_{sham}$ group and 11 participants allocated to the MST+tDCS group (Figure 3.3). Individual participant characteristics at baseline are presented in Table 3.1. Documented adverse events during the study have been reported previously (Evans & Field-Fote, 2022) and included cases of mild-to-moderate headache following tDCS and delayed-onset muscle soreness following MST. There were no between-groups differences in MST duration, $t(23)$=-0.13, p=0.90, or intensity, $t(23)$=-

0.25, p=0.80. Mean MST duration and intensity for the full study sample was 37 minutes (SD=6.1) and 51.9% HRR (SD=14.3), respectively. Individual and group mean training duration at each intervention time point have been reported previously (Evans & Field-Fote, 2022).

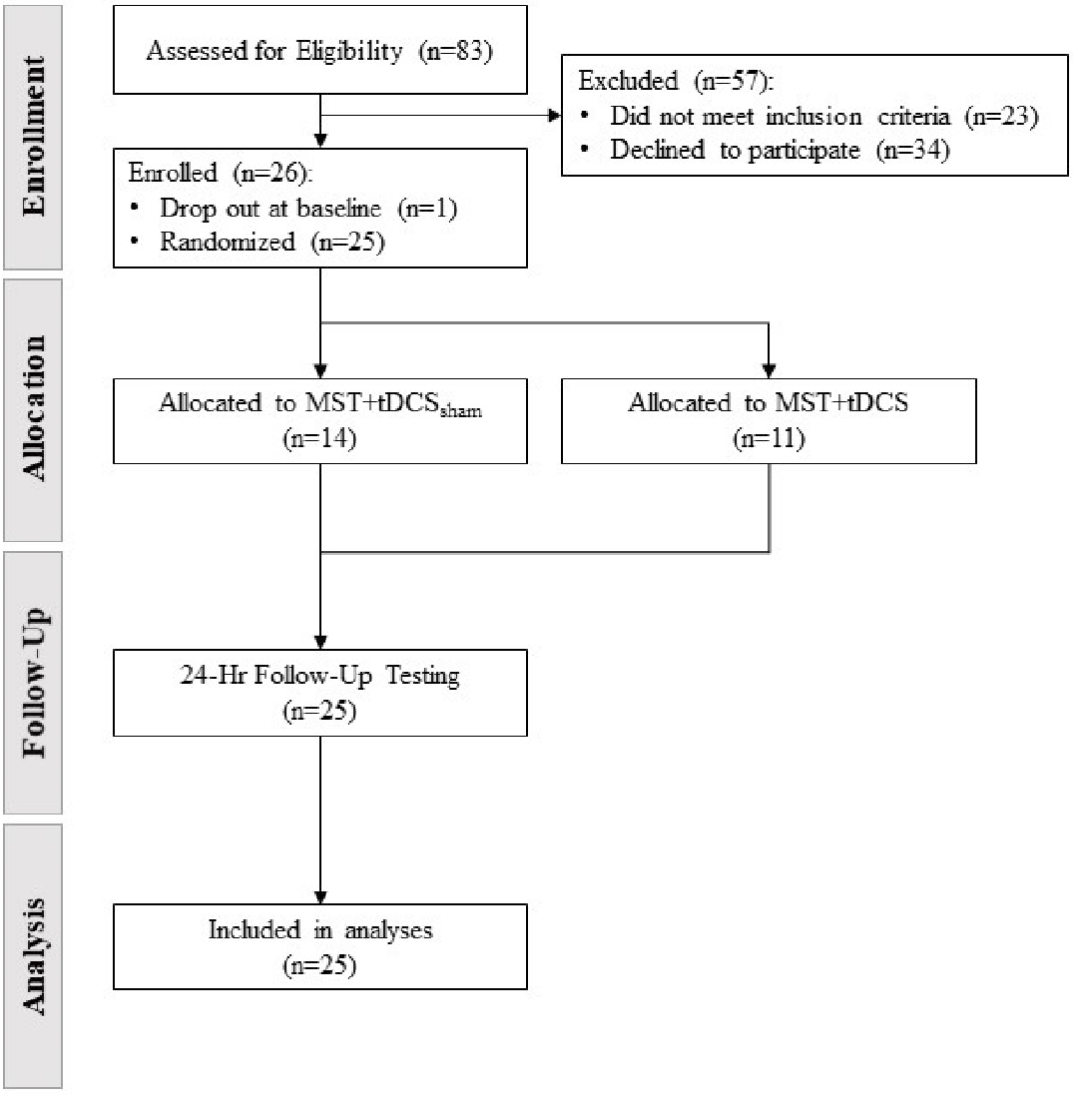


Figure 3.3. Recruitment, enrollment, and group allocation flow diagram.

Table 3.1. Individual participant characteristics according to intervention group at baseline.

Intervention Group	Participant	Sex	Age	BMI	TSI	NLI	AIS	LEMS	GXT HR_{peak}	GXT VO_{2peak}	Walking Speed (m/s)	Antispasmodics
$MST+tDCS_{sham}$	01	F	19	19.6	12	C7	D	40	141	18.9	1.27	Yes
	02	M	37	22.4	228	C7	D	45	151	27.5	1.43	Yes
	03	M	55	26.6	12	C5	D	35	134	24.5	0.20	No
	04	M	58	19.4	46	C5	D	48	107	15.1	1.32	Yes
	05	F	33	18.6	115	C4	D	28	116	14.0	0.66	Yes
	06	M	56	27.2	98	C5	D	49	180	24.5	1.84	Yes
	07	M	20	26.6	24	C5	D	30	153	21.8	0.31	Yes
	08	M	50	23.3	236	C5	D	43	112	11.4	0.18	No
	09	M	60	29.9	35	C5	D	47	152	11.2	0.82	No
	10	M	54	31.1	12	C4	D	31	115	13.6	0.50	Yes
	11	M	51	25.5	32	C4	D	32	110	12.0	0.36	Yes
	12	F	63	18.6	65	T8	D	25	145	22.0	0.30	Yes
	13	M	36	21.3	202	C6	D	22	153	18.4	0.47	Yes
	14	F	62	15.8	188	C4	C	45	110	10.3	0.47	No
	Mean (SD)	**N/A**	**46.7 (15.0)**	**23.3 (4.6)**	**93.2 (85.3)**	**N/A**	**N/A**	**37.1 (9.2)**	**134.2 (22.7)**	**17.5 (5.8)**	**0.72 (0.53)**	**N/A**
MST+tDCS	01	F	48	20.6	42	T6	D	39	127	22.9	0.62	Yes
	02	M	44	25.7	246	C6	D	36	124	24.8	0.20	Yes
	03	M	50	19.3	276	C5	D	30	125	14.7	0.07	Yes
	04	M	49	30.4	31	C4	D	50	167	21.7	1.77	Yes
	05	M	45	25.9	22	C4	C	26	112	16.2	0.87	Yes
	06	F	29	19.8	11	T8	D	42	154	14.7	0.73	No
	07	M	47	39.6	11	C4	D	49	101	7.3	0.86	Yes
	08	M	69	27.8	24	C4	D	47	143	13.9	0.45	Yes
	09	M	51	30.9	75	C4	D	36	123	13.8	0.07	Yes
	10	M	64	25.1	66	C7	D	48	115	15.7	0.34	Yes
	11	F	59	21.0	59	C7	D	49	104	12.8	1.09	Yes
	Mean (SD)	**N/A**	**50.5 (10.7)**	**26.0 (6.1)**	**78.5 (93.0)**	**N/A**	**N/A**	**41.1 (8.3)**	**126.8 (20.5)**	**16.2 (5.0)**	**0.64 (0.51)**	**N/A**

Abbreviations: $MST+tDCS_{sham}$, *motor skill training plus sham transcranial direct current stimulation*; MST+tDCS, *motor skill training plus active transcranial direct current stimulation*; M, *male*; F, *female*; BMI, *body mass index* (m/kg^2); TSI, *time since injury* (months at enrollment); NLI, *neurological level of injury*; AIS, *American Spinal Injury Association Impairment Scale classification*; LEMS, *lower extremity motor score* (combined limbs); GXT HR_{peak}, *graded exercise test peak heart rate* (bpm); GXT VO_{2peak}, *graded exercise test peak oxygen uptake* (ml/kg/min).

3.3.2 Outcomes

3.3.2.1 Walking Measures

Overground Walking Speed

Analyses revealed a significant effect of TIME on walking speed, $F(7,161)=11.69$, $p<0.001$. Neither GROUP nor TIMExGROUP interaction contributed to differences. In the absence of between-groups or interaction effects, post hoc comparisons for the main effect of TIME were performed for the full study sample. Post hoc comparisons revealed a significant increase in walking speed that persisted from D1 (M=0.69 m/s, SD=0.51) to D5 (M=0.82 m/s, SD=0.51), $t(24)=4.98$, $p<0.001$. A significant increase in walking speed was also observed over the 3-day intervention period from $D2_{pre}$ (M=0.75 m/s, SD=0.50) to $D4_{post}$ (M=0.81 m/s, SD=0.50), $t(24)=3.05$, $p=0.006$. Responsiveness of walking speed to intervention over the 5-day study period was large ($ES=1.04$).

Paired comparisons of between-day time points revealed a significant increase in walking speed from D1 to $D2_{pre}$ (M=0.75 m/s, SD=0.50), $t(24)=3.78$, $p=0.001$, and from $D2_{post}$ (M=0.75 m/s, SD=0.50) to $D3_{pre}$ (M=0.78 m/s, SD=0.48), $t(24)=2.36$, $p=0.027$. There were no differences in walking speed for within-day time points. Cumulative between-day change accounted for 84.6% of the overall change in walking speed from D1 to D5 ($\Sigma\Delta M=0.11$ m/s, SD=0.19), while within-day change accounted for 15.4% of the total change ($\Sigma\Delta M=0.02$ m/s, SD=0.14). Differences in cumulative within-day and between-day change were not statistically significant. Group-level paired comparisons of walking speed for the $MST+tDCS_{sham}$ and MST+tDCS groups, along with the full study

sample, are presented in Figure 3.4. Within-day and between-day change in walking speed is reported in Table 3.2.

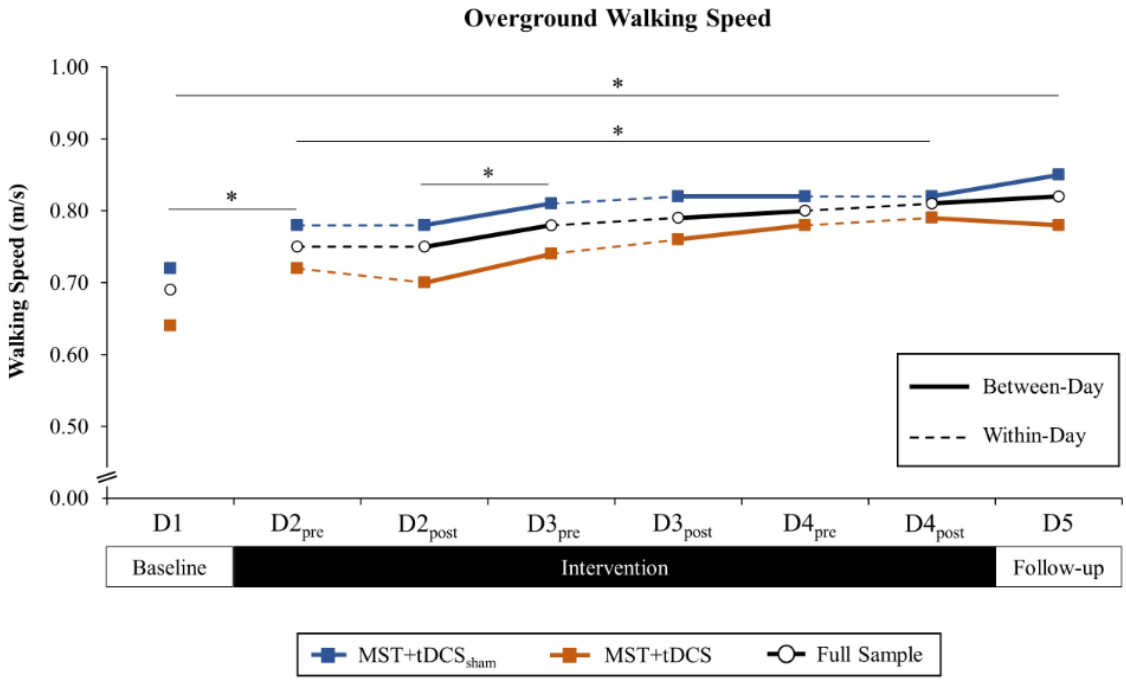


Figure 3.4. Overground walking speed (m/s) across all time points among the MST+tDCS$_{sham}$ group (blue line with square marker), MST+tDCS group (orange line with square marker), and the combined study sample (black line with circle marker). Solid lines indicate between-day (offline) and hashed lines indicate within-day (online) time intervals during the intervention period. No between-groups differences were observed. *Significant difference between time points for the combined study sample (p<0.10).

Cadence and stride length

Analyses revealed a significant effect of TIME on cadence, $F(7,160)=12.71$, $p<0.001$, stronger limb stride length, $F(7,160)=10.31$, $p<0.001$, and weaker limb stride length, $F(7,160)=9.73$, $p<0.001$. There were no effects of GROUP or TIMExGROUP interaction on cadence or stride length of the stronger or weaker limb. Failing to observe between-groups differences or interaction effects, post hoc analyses were performed using data from the full study sample.

Post hoc analyses revealed a significant increase in cadence that persisted from D1 (M=72.5 strides/min, SD=35.5) to D5 (M=81.8 strides/min, SD=34.2), $t(24)=5.13$, $p<0.001$. Analyses of the 3-day intervention period revealed a significant increase in cadence from $D2_{pre}$ (M=76.7 strides/min, SD=33.8) to immediately following intervention at $D4_{post}$ (M=81.2 strides/min, SD=34.6), $t(24)=3.19$, $p=0.004$. Paired comparisons of between-day time points revealed significant increases in cadence from D1 to $D2_{pre}$, $t(24)=2.70$, $p=0.012$, and from $D2_{post}$ (M=77.1 strides/min, SD=34.0) to $D3_{pre}$ (M=79.1 strides/min, SD=33.2), $t(24)=2.19$, $p=0.039$. There were no within-day differences in cadence. Differences in cumulative within-day and between-day change were not significant.

Significant increases were observed for stronger limb stride length from D1 (M=101.3 cm, SD=32.9) to D5 (M=109.8 cm, SD=32.2), $t(24)=4.58$, $p<0.001$, and for weaker limb stride length from D1 (M=101.5 cm, SD=33.3) to D5 (M=110.2 cm, SD=32.2), $t(24)=4.79$, $p<0.001$. Analyses of the 3-day intervention period revealed a significant increase in stronger stride length from $D2_{pre}$ (M=107.1 cm, SD=32.1) to immediately following intervention at $D4_{post}$ (M=110.1 cm, SD=31.4), $t(24)=2.06$, $p=0.051$, as well as weaker stride length from $D2_{pre}$ (M=107.2 cm, SD=32.1) to $D4_{post}$ (M=110.4 cm, SD=31.7), $t(24)=2.05$, $p=0.051$. Pairwise comparisons of between-day time points for stronger limb stride length revealed significant increases from D1 to $D2_{pre}$, $t(24)=4.00$, $p=0.001$, and from $D2_{post}$ (M=106.4 cm, SD=31.7) to $D3_{pre}$ (M=109.0 cm, SD=30.7), $t(24)=2.25$, $p=0.034$. Likewise, between-day increases in weaker limb stride length were observed from D1 to $D2_{pre}$, $t(24)=4.01$, $p=0.001$, and from $D2_{post}$ (M=106.0 cm, SD=31.4) to $D3_{pre}$ (M=109.0 cm, SD=31.1), $t(24)=2.57$, $p=0.017$. There were no

within-day differences in stride length for the stronger or weaker limbs. Furthermore, differences in cumulative within-day and between-day change were not significant. Paired comparisons of cadence and stride length for the full study sample are reported in Table 3.2.

TLA and ACC

Analyses revealed a significant effect of TIME, $F(7,161)=3.10$, $p<0.01$, but no effect of GROUP or TIMExGROUP interaction on stronger limb TLA (Appendix B.3). There was no effect of TIME, GROUP, or TIMExGROUP interaction on weaker limb TLA (Appendix B.4). Analyses revealed a significant effect of TIME on stronger limb ACC, $\chi^2(7)=24.22$, $p=0.001$, and weaker limb ACC, $\chi^2(7)=23.40$, $p=0.001$. There were no GROUP differences in change in stronger or weaker limb ACC across time points. In the absence of GROUP differences, post hoc analyses for stronger limb TLA and weaker and stronger limb ACC were carried out using the full study sample.

Post hoc analyses revealed a significant increase in stronger limb TLA that persisted from D1 (M=19.2°, SD=4.5) to D5 (M=20.5°, SD=3.9), $t(24)=2.42$, $p=0.023$. There were no differences in stronger TLA from $D2_{pre}$ to immediately following intervention at $D4_{post}$. Pairwise comparisons of between-day time points revealed a significant decrease in stronger limb TLA from $D3_{post}$ to $D4_{pre}$ (M=20.2°, SD=3.9), $t(24)=-2.25$, $p=0.034$, while within-day comparisons revealed a significant increase from $D3_{pre}$ (M=20.1°, SD=4.5) to $D3_{post}$ (M=20.9°, SD=3.4), $t(24)=2.29$, $p=0.031$.

Post hoc analyses revealed a significant increase in weaker limb ACC that persisted from D1 (Md=0.91, IQR=0.82-0.94) to D5 (Md=0.93, IQR=0.88-0.96), Z=-2.53, p=0.011. Individual participant relative motion plots at D1 and D5 used to calculate the ACC are provided in Appendix B.5. Differences in weaker ACC were not significant from $D2_{pre}$ to $D4_{post}$. There were no differences in stronger limb ACC from D1 to D5 or from $D2_{pre}$ to $D4_{post}$. Pairwise comparisons of between-day time points revealed a significant increase in weaker limb ACC from D1 to $D2_{pre}$ (Md=0.93, IQR=0.87-0.95), Z=-2.93, p=0.003, and from $D2_{post}$ (Md=0.92, IQR=0.87-0.95) to $D3_{pre}$ (Md=0.92, IQR=0.88-0.96), Z=-2.26, p=0.024. There were no within-day differences in weaker limb ACC. Pairwise comparison of between-day time points revealed a significant increase in stronger limb ACC from $D2_{post}$ (Md=0.93, IQR=0.89-0.95) to $D3_{pre}$ (Md=0.94, IQR=0.91-0.95), Z=-2.01, p=0.045, and a decrease from $D3_{post}$ (Md=0.94, IQR=0.92-0.96) to $D4_{pre}$ (Md=0.93, IQR=0.91-0.95), Z=-2.08, p=0.037. There were no within-day differences in stronger limb ACC. Paired comparisons of TLA (stronger limb) and ACC (weaker limb) for the full study sample are presented in Figure 3.5/Table 3.2.

Table 3.2. Between-day (blue columns), within-day (white columns), and cumulative (orange column) change in outcomes across time intervals.

	Time Intervals							
	Baseline	**Intervention**					**24-Hr Follow-up**	**Cumulative**
Outcomes	$\Delta D1\text{-}D2_{pre}$	$\Delta D2_{pre}\text{-}D2_{post}$	$\Delta D2_{post}\text{-}D3_{pre}$	$\Delta D3_{pre}\text{-}D3_{post}$	$\Delta D3_{post}\text{-}D4_{pre}$	$\Delta D4_{pre}\text{-}D4_{post}$	$\Delta D4_{post}\text{-}D5$	$\Delta D1\text{-}D5$
Walking Speed (m/s)	**0.06* (0.08) *p*=0.001**	0.00 (0.07) *p*=0.740	**0.03* (0.07) *p*=0.027**	0.02 (0.05) *p*=0.160	0.01 (0.08) *p*=0.728	0.01 (0.07) *p*=0.502	0.01 (0.09) *p*=0.704	**0.13* (0.13) *p*<0.001**
Cadence (strides/min)	**4.2* (7.7) *p*=0.012**	0.5 (4.3) *p*=0.605	**2.0* (4.6) *p*=0.039**	0.8 (3.8) *p*=0.295	0.9 (5.8) *p*=0.484	0.3 (5.1) *p*=0.687	0.6 (5.6) *p*=0.600	**9.3* (9.1) *p*<0.001**
SL-Weaker (cm)	**5.7* (7.1) *p*<0.001**	-1.2 (6.5) *p*=0.361	**3.0* (5.8) *p*=0.017**	1.2 (5.2) *p*=0.251	-0.4 (5.2) *p*=0.708	0.4 (4.5) *p*=0.552	0.0 (5.2) *p*=0.899	**8.7* (9.1) *p*<0.001**
SL-Stronger (cm)	**5.8* (7.3) *p*<0.001**	-0.7 (6.4) *p*=0.579	**2.6* (5.7) *p*=0.034**	1.4 (4.7) *p*=0.133	-0.7 (5.2) *p*=0.516	0.3 (4.9) *p*=0.723	-0.2 (6.3) *p*=0.797	**8.3* (9.0) *p*<0.001**
TLA-Weaker (°)	**0.75* (2.1) *p*=0.081**	-0.22 (2.9) *p*=0.716	0.57 (2.5) *p*=0.259	-0.12 (1.8) *p*=0.738	0.13 (1.8) *p*=0.723	0.16 (1.4) *p*=0.580	**-0.61* (1.5) *p*=0.052**	0.67 (2.8) *p*=0.237
TLA-Stronger (°)	0.95 (2.8) *p*=0.104	-0.18 (1.8) *p*=0.619	0.10 (1.9) *p*=0.787	**0.86* (1.9) *p*=0.031**	**-0.80* (1.7) *p*=0.026**	0.48 (1.5) *p*=0.129	-0.07 (1.6) *p*=0.829	**1.34* (2.8) *p*=0.023**
ACC-Weaker	**0.02* (0.00-0.05) *p*=0.003**	0.00 (-0.03-0.01) *p*=0.129	**0.01* (-0.01-0.03) *p*=0.024**	0.00 (0.00-0.02) *p*=0.378	-0.01 (-0.02-0.03) *p*=0.125	0.00 (-0.01-0.02) *p*=0.551	0.00 (-0.01-0.01) *p*=0.843	**0.01* (0.00-0.43) *p*=0.011**
ACC-Stronger	0.01 (-0.01-0.01) *p*=0.278	0.00 (-0.01-0.02) *p*=0.537	**0.01* (0.00-0.02) *p*=0.045**	0.00 (-0.01-0.02) *p*=0.249	**-0.01* (-0.02-0.01) *p*=0.037**	0.01 (-0.02-0.02) *p*=0.586	-0.01 (-0.02-0.01) *p*=0.180	0.01 (-0.02-0.01) *p*=0.637
BBS (total score)								**2.0* (3.7) *p*=0.010**
FES-I (total score)								**-2.6* (3.8) *p*=0.002**

Note: ACC reported as median (IQR). All other outcomes reported as mean (SD). *Significant difference between time points (*p* values for walking speed, cadence, stride length, TLA, BBS, and FES-I derived from paired-samples t-test; *p* values for ACC derived from Wilcoxon signed-rank test). Abbreviations: SL-Weaker, *weaker limb stride length*; SL-Stronger, *stronger limb stride length*; TLA-Weaker, *weaker limb trailing limb angle*; TLA-Stronger, *stronger limb trailing limb angle*; ACC-Weaker, *weaker limb angular component of the coefficient of correspondence*; ACC-Stronger, *stronger limb angular component of the coefficient of correspondence*; BBS, *Berg Balance Scale*; FES-I, *Falls-Efficacy Scale-International* version.

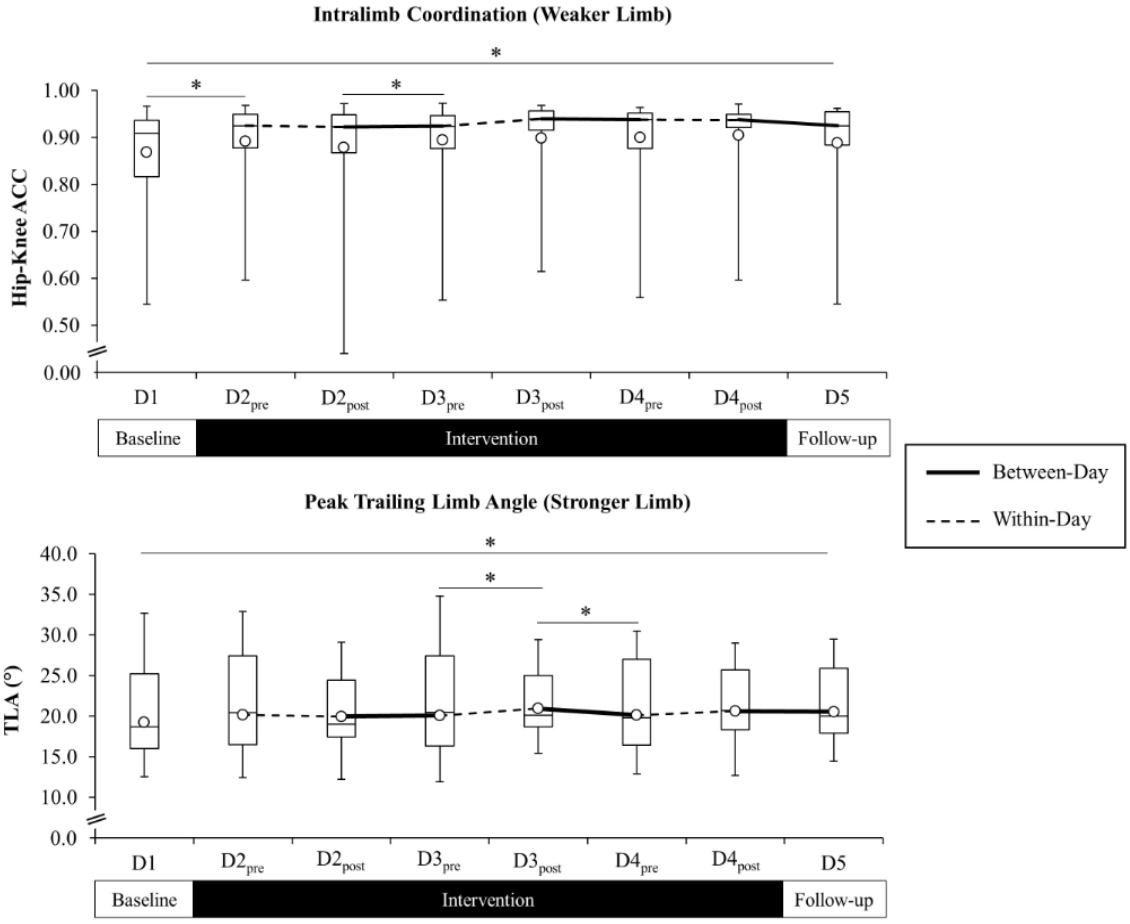


Figure 3.5. Weaker limb intralimb coordination (ACC) [top figure] and stronger limb trailing limb angle (TLA) [bottom figure] across all time points for the combined study sample. Open circle markers represent the mean at each time point. Solid lines indicate between-day (offline) and hashed lines indicate within-day (online) time intervals during the intervention period. *Significant difference between time points (p<0.10). Higher ACC values indicate improved cycle-to-cycle intralimb coordination (ACC=1.0 indicates perfect cycle-to-cycle consistency in hip-knee relative motion).

Balance function

Analyses revealed a significant effect of TIME on the BBS, $F(1,23)=7.16$, $p=0.01$, and FES-I, $F(1,23)=12.43$, $p<0.01$. There was no effect of GROUP or TIMExGROUP interaction for either measure. Results of LMM analysis for the BBS and the FES-I are reported in Appendices B.6 and B.7, respectively. In the absence of between-groups differences or interaction effects, post hoc analyses for the BBS and FES-I were carried out for the full study sample. Pairwise comparisons revealed a significant increase in BBS total score from D1 (M=39.0, SD=14.2) to D5 (M=41.1, SD=13.3), $t(24)=2.78$, $p=0.01$, and a decrease in FES-I total score from D1 (M=35.3, SD=10.2) to D5 (M=32.6, SD=8.8), $t(24)=-3.52$, $p<0.01$. Paired comparisons of the BBS and FES-I for the full study sample are presented in Figure 3.6/Table 3.2.

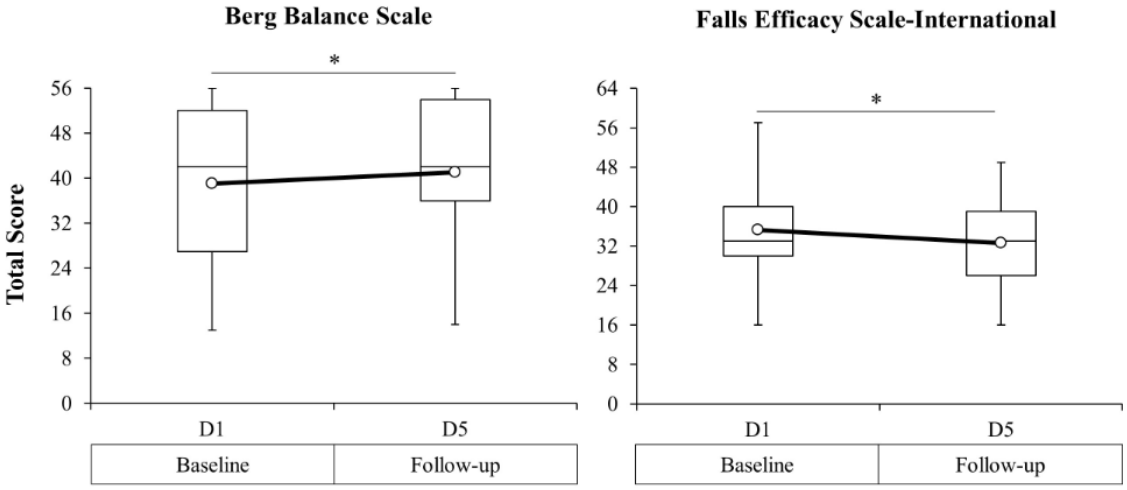


Figure 3.6. Berg Balance Scale (BBS) total score [left figure] and Falls Efficacy Scale-International (FES-I) total score [right figure] from baseline (D1) to 24-hours post-intervention (D5) for the combined study sample. Open circle markers represent the mean at each time point. *Significant difference between time points ($p<0.10$). Higher BBS scores indicate improved balance function. Lower FES-I scores indicate decreased self-reported fear of falling.

3.4 Discussion

We examined the effects of a 3-day moderate-intensity MST program on measures of walking and balance function in participants with MISCI. Participation in brief MST was associated with significant increases in overground walking speed, cadence, bilateral stride length, stronger limb TLA, and weaker limb ACC. Measures of balance function and perceived fear of falling were also improved. We further examined whether combining MST with tDCS would lead to greater improvements in outcomes compared to MST alone. Concurrent application of tDCS failed to produce greater improvements in walking and balance function compared to MST plus sham tDCS. MST was associated with change in the primary outcome (walking speed) approaching or exceeding observations in longer-term locomotor training studies. Furthermore, among those walking outcomes that were positively influenced by MST intervention, between-day (offline) effects contributed to a greater percentage of total change in outcomes compared to within-day (online) effects.

3.4.1 Improved walking performance following brief MST

Several randomized clinical trials involving various multi-week locomotor training interventions have reported improvements in overground walking speed ranging from 0.01–0.16 m/s (Alexeeva et al., 2011; Field-Fote & Roach, 2011; Jones et al., 2014b; Kapadia et al., 2014; Lotter et al., 2020). Despite the brief 3-day training period of our intensive MST program, our findings were comparable to these prior studies (i.e., Δ walking speed = 0.13 m/s), although the magnitude of change did not reach the minimally clinically important difference of 0.15 m/s previously reported in this population (Forrest

et al., 2014). Major limitations of prior investigations are the time and resources (e.g., capital, technology, personnel) needed to deploy the interventions. We investigated a motor skill training circuit of locomotor-related activities that required little to no equipment and could feasibly be implemented with supervision in the home or community. The MST program encouraged ballistic, cyclic volitional movement sequences that provoked a moderate-intensity cardiovascular response. These features of the MST circuit contrast with prevailing locomotor training approaches that emphasize guided massed practice stepping on a treadmill, either with or without bodyweight support or robotic assistance (Field-Fote & Roach, 2011; Hannold et al., 2006; Merholz et al., 2012). Aside from limitations on accessibility, these approaches often constrain the individual's ability to actively explore motor solutions needed to successfully manage "real-world" environmental conditions (Mutha et al., 2011), such as the need to rapidly modulate step speed while traversing a crosswalk or modulating step height to successfully navigate a curb. While in our study the MST circuit was delivered in a clinical laboratory setting with single person providing all supervision, the magnitude of improvement in overground walking speed over a short intervention period suggests value in further investigation. The MST intervention may be a viable supplement or alternative to locomotor training in cases where time and/or available resources limit participation.

In addition to improvements in walking speed, participation in three days of MST was associated with significant increases in stride frequency (cadence) and length. Gait kinematics associated with walking impairments in persons with SCI have been reported extensively (Ardestani et al., 2019; Awai & Curt, 2014; Field-Fote & Tepavac, 2002; Nooijen et al., 2009; Pepin et al., 2003; Sohn et al., 2018). Both stride frequency and stride

length are coupled to walking speed modulation in non-injured adults (van Hedel et al., 2006). In persons with SCI, muscle weakness and diminished capacity to produce high-velocity muscle actions of the lower limbs limits maximal walking speed, primarily through an effect on reduced cadence (Pepin et al., 2003). In a 12-week stratified, randomized study comparing four different overground and treadmill-based locomotor training strategies, both cadence and bilateral stride length were increased, regardless of approach (Nooijen et al., 2009). We observed an increase in cadence of 9.3 strides/min following only three days of training, which was comparable to the most effective approach examined in the previous study (i.e., overground training; 10.0 strides/min) and superior to all other modes of training examined (i.e., treadmill-based training; 3.0-7.8 strides/min).

Motor training interventions that emphasize high-velocity, ballistic volitional actions, as opposed to repetitive, constant velocity movements, may provide a more robust stimulus for increasing stride frequency in persons with SCI. In a case series report of PwMISCI, 12-weeks of lower extremity resistance and ballistic plyometric training was associated with an increase in bilateral stride length but not cadence (Gregory et al., 2007). Failure of ballistic training to increase cadence in the case series report could be attributed to higher average baseline walking speeds among their small cohort (M = 1.08 m/s) compared to our sample (M = 0.69 m/s) as prior evidence suggests that maximal cadence plateaus as walking speeds approach 1.0 m/s in this population (Pepin et al., 2003). Longer training studies are needed to determine whether there is a ceiling effect for cadence following prolonged exposure to our MST circuit.

In addition to cadence and stride length, modulation of walking speed, in particular the transition from slow to fast walking, is aided by the individual's ability to alter

propulsive forces during locomotion (Peterson et al., 2011). In aging adults, smaller propulsive forces and an increased emphasis on more proximal leg muscles for power generation are associated with diminished walking capacity (i.e., speed and distance) (Browne & Franz, 2018). In persons with stroke (Awad et al., 2015; Awad et al., 2020; Peterson et al., 2010) and SCI (Peters et al., 2018), impaired central drive (Awad et al., 2020; Bravo-Esteban et al., 2015; Wirth et al., 2008b) and muscle weakness (DiPiro et al., 2015; Roelker et al., 2019) contribute to decreased magnitude and rate of lower limb force development, culminating in diminished propulsive impulse and slower walking speeds. Interventions that increase corticospinal drive and facilitate volitional ability to rapidly recruit muscles of locomotion may enhance propulsive force generation and improve the capacity to modulate walking speed. Trailing limb angle has been validated as a surrogate measure of propulsive force in healthy adults (Hsiao et al., 2015) and individuals post-stroke (Lewek & Sawicki, 2019). To our knowledge, we are the first to characterize the effects of motor training on TLA during overground walking in PwMISCI.

Baseline peak TLA of the stronger and weaker limbs among our sample (M = 19.2°) were lower than previous reports in non-injured adults (M = 26.3°) (Miyazaki et al., 2019). Three days of ballistic, cyclic MST was associated with a significant increase in stronger but not weaker TLA. The magnitude of change in stronger TLA (ΔM = 1.3°) is comparable to a 12-week study in persons with stroke, where treadmill and overground locomotor training was associated with an increase in both paretic and non-paretic TLA of approximately 2° (Hsiao et al., 2016). Ballistic training involving rapid, explosive muscle contractions is associated with greater task-specific adaptations compared to low-velocity training (Cordner et al., 2021; Tschopp et al., 2011). Increased corticospinal drive

(Schubert et al., 2008), earlier onset motor unit activation (Van Cutsem et al., 1998), increased Type II muscle fiber recruitment (Wilson et al., 2012), and increased rate of force development (Del Vecchio et al., 2019) are aspects of ballistic training that may support improved forward propulsion kinematics and facilitate walking speed modulation in persons with motor deficits. These features of training may account for the comparable changes in TLA we observed despite the marked differences in training mode and duration; however, the effects of the MST circuit in PwMISCI may be restricted to the less impaired limb, where greater corticospinal tract preservation may contribute to enhanced ability to modulate lower limb kinematics (Hope et al., 2020). Although evidence in non-injured adults suggests that even small-scale changes in TLA (i.e., $\Delta = 1.5°$) can contribute to as much as 65% of the increase in propulsive force generated during slow to fast walking (Hsiao et al., 2015), it is unclear whether the modest increase in TLA we observed was consequential to increases in walking speed among our participants. Further analysis is needed to uncover potential relationships between changes in TLA and walking speed in this population.

Prior investigations have examined intralimb coordination (hip-knee ACC) as a measure of the integrated function of motor systems involved in cyclic locomotor behavior in persons with SCI (Awai & Curt, 2014; Field-Fote & Tepavac, 2002; Tepavac & Field-Fote, 2001). In a case series report, up to 40 sessions of treadmill and overground step training was associated with both positive and negative changes in weaker limb ACC (Δ range = -0.07-0.17) (Holleran et al., 2018). We observed similar results among our larger sample following three days of MST (Δ range = -0.01-0.13), indicating a similar degree of variability in responsiveness among participants, regardless of training mode or duration.

In a 12-week study of treadmill-based locomotor training combined with peroneal nerve stimulation, 64% of participants (9/14) demonstrated improved intralimb coordination of the weaker limb with an average increase in ACC of 0.09 (Field-Fote & Tepavac, 2002). Our findings were comparable in that 68% of participants (17/25) demonstrated improvements in weaker limb ACC, albeit the mean change among our sample was smaller ($\Delta M = 0.03$). Finally, 36-sessions of high-intensity treadmill training was associated with a non-significant increase in weaker limb ACC ($\Delta M = 0.04$) (Leech et al., 2016). We observed a significant increase in median weaker limb ACC ($\Delta Md = 0.01$), with mean change being comparable to the latter study.

In light of the above, we draw three conclusions concerning intralimb coordination. First, response of weaker limb ACC to training was similar in terms of range and magnitude of change reported across studies, regardless of training approach. This suggests that adaptation of cycle-to-cycle intralimb coordination in PwMISCI is not limited to participation in treadmill-based massed practice stepping protocols and that alternative motor training approaches may yield similar benefits. Second, although we observed a sample-wide increase in weaker limb ACC, the magnitude of change was small and not all participants demonstrated improvement. Moreover, we failed to observe a change in stronger limb ACC. It is likely that responsiveness to training is participant and limb dependent and may be contingent upon one or more individual characteristics, such as the degree of preserved lower limb motor function, presence and severity of spasticity, and/or baseline functional capacity. In fact, there was marked heterogeneity among participants both within and between studies in terms of baseline LEMS, walking speeds, and ACC, which could account for the variable responses. Finally, the consistent finding of limited

and modest ranges of responses among the present and prior studies suggests that intralimb coordination may not be easily altered with motor training despite significant change in other measures of walking ability. For example, we observed marked increases in stride frequency and stride length that coincided with significant increases in overground walking speed, yet cycle-to-cycle intralimb coordination was little changed. This could indicate that the ongoing coordination, relative timing, and maintenance of lower limb segment positions is generally conserved, even in the face of significant changes in other kinematic variables important for walking speed modulation; however, it is possible that coordination between more distal limb segments (i.e., knee-ankle ACC) may have been influenced by MST, but this was not quantified in the present study and, therefore, may represent a meaningful focus for future examination.

3.4.2 Improved balance and reduced fear of falling following brief MST

Participation in three consecutive days of MST was associated with significant improvements in balance function (increased BBS scores) and reduced fear of falling (decreased FES-I scores). Muscle weakness, impaired balance, and concern for falling contribute to a higher frequency of falls among individuals with SCI who are ambulatory (Jorgensen et al., 2017; Kahn et al., 2019). Enhanced balance performance is associated with improved overground walking ability, reduced incidence of falls, and enhanced confidence in performing activities of daily living (Datta et al., 2009; Forrest et al., 2012; Singh et al., 2021). The finding that brief MST was associated with a significant improvement in balance is consistent with longer-term training interventions in participants with MISCI (Houston et al., 2020; Morrison et al., 2018; Neville et al., 2019; Stevens et

al., 2015), although the magnitude of change we observed (ΔBBS = 2.0) was smaller than these previous reports (ΔBBS range = 4.5-13.0). Differences in the magnitude of change between studies may be due to heterogeneity in baseline motor function, time since injury at intervention onset, and total training duration. An important distinction between the present and prior interventions is the time, equipment, and personnel needed to realize improvements in balance performance. A longer-term study, including individuals with greater balance impairments, is needed to determine whether the magnitude of effect of the MST intervention on upright balance would be comparable to more traditional motor training approaches.

Despite existing evidence linking fear of falling with diminished functional walking capacity (Gabner et al., 2021), impaired balance (Wirz et al., 2010), and increased falls risk (Jorgensen et al., 2017), the effect of motor training on fear of falling has not been extensively characterized in PwMISCI (Abou et al., 2021). As a result, it is not clear how much improvement in the FES-I could be expected with training or to what extent changes in this measure are related to meaningful improvements in functional outcomes in this population (e.g., walking and balance performance). A single randomized controlled trial involving 6-weeks of thrice-weekly unsupported seated balance training was associated with a 2-point reduction in the FES-I (Boswell-Ruys et al., 2010); however, the effect of intervention was not different from a non-exercise control group. We observed a similar reduction in fear of falling (ΔFES-I = -2.6) that coincided with improvements in walking and balance function following 3 days of upright motor training, suggesting a possible relationship between the perception of falling and upright functional capacity. Further

investigation into the potential interaction between these outcomes following longer-term intervention would be of value.

3.4.3 tDCS did not augment effects of lower extremity motor training

Despite significant differences in walking and balance outcomes following brief MST, concurrent application of tDCS failed to augment the effects of training. Although existing evidence indicates that anodal tDCS applied to the motor cortex enhances corticospinal excitability in healthy adults and in persons with stroke (Bastani & Jaberzadeh, 2012), and that this effect supports mechanisms that promote motor skill acquisition and consolidation (Wittkopf et al., 2021), recent evidence suggests a high degree of interindividual variability in motor cortical responsiveness to tDCS (Jonker et al., 2021), which may have contributed to lack of effect in the present study. Furthermore, a recent meta-analysis examining effectiveness of active- versus sham tDCS on improving motor function after incomplete SCI revealed a significant but small effect in favor of active-tDCS (de Araujo et al., 2020); however, only five studies were included in the analysis and only two studies combined tDCS with lower extremity motor training (Kumru et al., 2016; Raithatha et al., 2016). Both studies applied tDCS in combination with robotic-assisted treadmill training, and while improvements in walking ability were observed in both studies, neither reported between-groups differences in outcomes. Our findings are consistent with these previous reports as equivalent improvements in walking ability were observed in both the MST+tDCS and MST+$tDCS_{sham}$ groups.

There may be several reasons for our failure to observe effects of tDCS. First, damage to spinal tracts is highly heterogeneous even among persons with similar injury classification; as such, differences in extent of corticospinal tract damage among participants may have influenced individual responsiveness to tDCS. The increased corticomotor excitability associated with anodal tDCS is believed to augment volitional motor control by increasing descending drive (Nitsche & Paulus, 2000). The extent of damage to descending tracts may have limited transmission between cortical and spinal circuits in our sample. Future studies may be improved by use of motor-evoked potentials as a probe of responsiveness to corticomotor stimulation (Labruna et al., 2019) and to stratify individuals according to responders and non-responders based on the magnitude of these evoked responses. Second, our measures of motor function (i.e., walking and balance outcomes) may not have been sufficiently sensitive to capture more discrete changes in volitional motor actions previously reported to be influenced by acute changes in corticospinal excitability. For example, the motor cortex drives the ankle dorsiflexors on a step-by-step basis during bipedal walking (Peterson et al., 2012), and a single session of tDCS applied to the motor cortex is associated with enhanced ankle control in participants with MISCI (Yamaguchi et al., 2016). In the present study, if tDCS did influence ankle motor control, the effect did not manifest as improved responses in walking and balance performance among participants who received active tDCS. Based on our findings, combining MST with tDCS did not confer greater advantage on lower extremity motor tasks involving upright mobility compared to MST alone.

3.4.4 Within-day (online) versus between-day (offline) effects

It is well-documented that training-induced procedural learning is achieved through a combination of online (acquisition [within-day]) and offline (consolidation [between-day]) processes (Dayan & Cohen, 2011; Robertson et al., 2004). This study is the first to characterize within-day and between-day changes in walking outcomes over multiple consecutive days of lower extremity motor training in PwMISCI, and to assess the effect if adding tDCS. Offline effects of intensive MST accounted for the largest percentage of total change in walking speed, cadence, and stride length. In addition, change in these measures was only observed during offline time intervals. These effects were not further influenced by the addition of tDCS.

Aerobic exercise and non-invasive brain stimulation have each been explored as potential neuromodulation approaches that have the capacity to reinforce mechanisms that subserve neuroplasticity and promote motor learning (Holman & Staines, 2021; Kim, Buchanan, et al., 2021; Nitsche, Schauenburg, et al., 2003; Singh, Neva, et al., 2014; Skriver et al., 2014). Intensive aerobic exercise facilitates neuroplasticity through various mechanisms, including enhanced blood flow to the motor cortex (Singh & Staines, 2015), upregulation of glucocorticoids (Milani et al., 2010) and neurotrophic factors (He et al., 2013), and increased states of arousal (McMorris et al., 2015). A single-session of moderate- to high-intensity aerobic exercise is associated with an increase in brain-derived neurotrophic factor (Mang et al., 2014), enhanced long-term potentiation-like plasticity (Singh, Neva, et al., 2014), and greater retention of skilled motor tasks (Holman & Staines, 2021). These processes are believed to augment motor skill training through an effect on motor program consolidation (offline processes) (Wanner et al., 2020). Likewise, anodal tDCS applied to the motor cortex induces changes in neuronal excitability that outlast the

stimulation period (Monte-Silva et al., 2013), and when combined with motor training, is believed to facilitate learning through NMDA-dependent long-term potentiation and an effect on motor skill consolidation (Cocco et al., 2018).

While intensive MST was associated with significant improvements in measures of walking performance that appeared to be reinforced during the 24-hours between training days, we failed to observe an additive effect of tDCS on either online or offline motor performance. The finding concerning lack of effect of tDCS on motor performance consolidation contrasts with prior motor training studies in non-injured adults. For example, both single session (Kim, Kim, et al., 2021) and multi-day (Reis et al., 2009) application of tDCS combined with upper limb motor training is associated with greater offline, but not online, improvements in motor performance when compared to sham tDCS. Likewise, in the lower limb, tDCS combined with motor training is associated with greater post-intervention (offline) improvements in a skilled stepping activity (Tseng et al., 2020) and a visuomotor tracking task (Sriraman et al., 2014) compared to sham stimulation. Despite these studies, there is a paucity of research investigating the temporal influence of tDCS on functional motor performance in persons with SCI, but our findings suggest that previous observations of offline consolidation effects of tDCS may not hold in this population.

It should be noted that much, but not all, of the offline change in walking outcomes following MST occurred between baseline (D1) and immediately prior to the first day of intervention on Day-2 ($D2_{pre}$). We propose two possible explanations to account for this observation. First, it is possible that the inclusion of a maximal aerobic exercise test at D1 facilitated processes that enhanced learning of the walking test at $D2_{pre}$. At baseline,

participants completed multiple bouts of fast walking, followed by upright standing balance tests, and ending with an intensive maximal graded exercise test to fatigue. Evidence highlighting the influence of intensive exercise on mechanisms that promote motor learning has been detailed in a previous section. It is possible that baseline aerobic exercise testing induced physiological mechanisms that augmented improvements in walking performance at $D2_{pre}$. It may be prudent in future studies to conduct aerobic exercise testing on a separate day from outcomes testing to avoid possible influence of acute exercise on subsequent tests of motor performance. Second, we cannot rule out presence of a simple learning effect wherein performing the walking test at D1 resulted in improved performance at $D2_{pre}$. Future studies may be improved by including multiple baseline assessments at different time points to establish stable pre-training levels of walking performance prior to intervention.

3.5 Limitations

Despite being the largest available study of intensive, high-velocity, volitional lower extremity motor training to improve walking outcomes in persons with SCI, and the largest study of tDCS to augment lower extremity function in this population, several limitations are considered. First, due to COVID-19 restrictions, our recruitment goal of 30 participants was not reached (n=25) and between-groups sample sizes were unbalanced, which may have contributed to an inability to detect between-groups differences; however, statistical modeling has indicated that, in pilot studies, a sample size of 12 participants per group is sufficient for estimating mean change and variability in outcomes (Julious, 2005). Even if

statistically significant between-groups differences were detected in the present study, it is doubtful that the magnitude of these differences would have been clinically meaningful. Second, mean baseline walking speed and total LEMS differed between groups, favoring the sham tDCS group in the former measure and the active tDCS group in the latter. Furthermore, these measures were higher among our participants compared to some prior studies. Existing evidence from individuals with SCI indicates that lower extremity strength is associated with walking speed (DiPiro et al., 2015), and baseline walking speed may be a predictor of responsiveness to training (Jones et al., 2014a). Third, various tDCS electrode montages have been proposed for modulating underlying neurophysiology, although the optimal montage has yet to be determined. The findings should be viewed within the context of the specific montage we used. Furthermore, it has been reported that sham tDCS may exert a small effect on corticospinal excitability (Dissanayaka et al., 2018); however, there is little evidence that transient shifts in neuronal excitability induced by sham stimulation are sufficient to produce changes in functional outcomes. Finally, the absence of a non-MST control group complicates interpretation of the unique contributions of the MST intervention. The addition of such a group could strengthen future studies.

3.6 Conclusions

Recovery of motor function, including walking and balance, is central to rehabilitation for PwMISCI and has implications for long-term health and independence for persons with motor deficits resulting from spinal injury. The time, effort, and costs associated with obtaining meaningful improvements in function after injury are of ongoing

interest. The MST circuit was designed to capitalize on the physiologic evidence for intensive training to activate neuroplastic mechanisms and to increase corticospinal drive through volitional engagement. Furthermore, the intent was to address limitations posed by traditional locomotor training approaches that emphasize slow, repetitive massed-practice stepping, lengthy training periods, and costly equipment that lacks long-term accessibility. While no effect of tDCS was identified, the cyclic, ballistic training activities appear to promote improvements in walking speed, relevant gait kinematics, and balance performance. Larger studies with longer training periods are needed to determine whether greater improvements in function can be realized.

CHAPTER 4. BRIEF HIGH-VELOCITY MOTOR SKILL TRAINING INCREASES STEP FREQUENCY AND IMPROVES LENGTH/FREQUENCY COORDINATION IN SLOW WALKERS WITH CHRONIC MOTOR-INCOMPLETE SPINAL CORD INJURY

4.1 Introduction

Improved mobility, including walking, is a priority among persons with SCI (Brown-Triolo et al., 2002), particularly among those who retain some residual motor function below the level of injury (Lo et al., 2016). Walking speed (WS) is a robust clinical measure used to assess functional mobility and predict future independence and long-term health outcomes (Fritz & Lusardi, 2009; Middleton et al., 2015). Consequently, the use of WS to evaluate functional progress and responsiveness to intervention is widespread in SCI rehabilitation and research (Bolliger et al., 2018; Field-Fote & Roach, 2011; Forrest et al., 2014; Jones et al., 2014b; Yang et al., 2014); however, WS alone reveals little about the specific motor strategies employed by persons with motor-incomplete SCI (PwMISCI) during walking or how the underlying characteristics of locomotor behavior may be influenced by intervention.

Walking speed reflects the interaction between step length (STL) and step frequency (SF). Under normal conditions, preferred WS is consistent with the step length-frequency combination that optimizes the energetic cost of locomotion (VanSwearingen & Studenski, 2014; Zarrugh et al., 1974). In fact, the ratio of STL to SF (termed the Walk Ratio [WR]) (Sekiya & Nagasaki, 1998) is stable across a wide range of walking speeds

(Bogen et al., 2018; Murakami & Otaka, 2017; Zijlstra et al., 1995), suggesting an underlying neuro-mechanical control mechanism that coordinates the amplitude and frequency of leg movements to optimize movement efficiency (Egerton et al., 2011; Saibene & Minetti, 2003). While WS provides a meaningful metric of overall walking capacity, the WR reflects the spatiotemporal coordination of rhythmic leg movements and the underlying motor control strategy used to optimize energetic efficiency at a given speed. Accordingly, deviations in the WR from values observed in non-pathological gait (Murakami & Otaka, 2017; Sekiya & Nagasaki, 1998) may be indicative of aberrant or sub-optimal locomotor control (Ambrus, Sanchez, et al., 2019; Kalron, 2016; Rota et al., 2011), while changes in the WR approaching these values may reflect improved spatiotemporal coordination and movement efficiency. Numerous motor training studies involving PwMISCI have reported increases in WS with concurrent increases in STL and/or SF (Ardestani et al., 2019; Gregory et al., 2007; Leech et al., 2016; Nooijen et al., 2009); however, to our knowledge, the interaction of these spatiotemporal parameters, as reflected by the WR, has yet to be characterized in this population.

After SCI, impaired central drive (Bravo-Esteban et al., 2015; Wirth et al., 2008a) and muscle loss below the level of injury (Dolbow & Gorgey, 2016) lead to marked decline in the magnitude and rate of lower extremity force development. The net effect is a diminution in stance phase propulsive force development (Peters et al., 2018) and reduced capacity to generate high SFs, in contrast to longer STLs (Pepin et al., 2003). We previously reported significant cumulative effects of a brief locomotor-related motor skill training (MST) circuit on overground WS and select gait kinematics (Evans & Field-Fote, 2022; Evans et al., 2022). The MST intervention was designed to address limitations of

existing locomotor training approaches (Barbeau et al., 1987; Hannold et al., 2006). For example, in treadmill walking, increasing the belt speed facilitates longer STLs but diminishes the need to generate higher SFs at a given walking speed (Dal et al., 2010; Hollman et al., 2016). Furthermore, the use of bodyweight support during training fails to directly replicate the peak ground reaction forces and propulsive impulses generated during non-weight supported activities (Apte et al., 2018; Elias et al., 2015). Apart from these limitations, overground locomotor training is often characterized by slower walking compared to the treadmill environment (Field-Fote et al., 2005), which fails to facilitate faster lower limb movement velocities during walking.

Given that individuals with SCI have limited capacity to increase SF relative to STL (Pepin et al., 2003), facilitating volitional rapid leg movements under full weightbearing conditions may be an important consideration for training. A unique feature of the MST intervention is the inclusion of high-velocity, cyclic movement patterns performed under full weight-bearing conditions. The intent of MST is to increase central drive to muscles of the lower extremities (Schubert et al., 2008), facilitate high rates of muscle force development (Van Cutsem et al., 1998; Wilson et al., 2012), and mimic the coordinated lower limb joint actions and joint angular velocities encountered during rapid overground ambulation. These features of the intervention may improve transferability of training effects by enhancing the ability, in the absence of bodyweight support, to produce higher SFs during overground walking.

In light of the above, the purpose of this analysis was to characterize the relationship between STL and SF, in terms of the WR, and to examine the effects of high-velocity MST on the interaction between changes in STL, SF, WS, and the WR in PwMISCI. It is

anticipated that, given the diminished capacity to produce high SFs along with a relatively intact ability to modulate STL, higher WR values would be observed among PwMISCI compared to prior reports in non-injured adults. Furthermore, we anticipated that MST emphasizing high-velocity lower limb movements would be associated with a decrease in the WR mediated in large part by improvements in the capacity to increase SF. Finally, in light of prior evidence demonstrating the WR constancy may be broken at slower speeds (Murakami & Otaka, 2017), we examined differences in outcomes that could be attributed to slow versus fast walking.

4.2 Methods

4.2.1 Study design

This study was part of a phase II, randomized intervention in which participants completed a MST circuit combined with concurrent application of either sham or active transcranial direct current stimulation (tDCS). The full study protocol and findings from the primary analyses have been published elsewhere (Evans & Field-Fote, 2022; Evans et al., 2022). The MST was associated with improvements in walking and balance function; however, the use of tDCS did not confer further benefits (Evans & Field-Fote, 2022). Here we explore relationships among walking outcomes from the full study sample and from a sub-group analysis of slow versus fast walkers. The study was carried out over five consecutive days (intervention on days 2, 3, 4). Walking assessments were completed each day: baseline, Day-1 (D1); pre-intervention, Day-2 (D2), Day-3 (D3), and Day-4 (D4); 24-hours post-intervention, Day-5 (D5).

4.2.2 Participants

The study protocol was approved by the Institutional Review Board at Shepherd Center (Atlanta, Georgia) in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study was registered prior to enrollment of the first participant (ClinicalTrials.gov: NCT03237234). Inclusion criteria for the study were chronic (≥12months) motor-incomplete SCI (American Spinal Injury Association Impairment Scale [AIS] C or D), at/above T10 neurological level, aged 18-70 years, able to stand for ≥5 minutes (with/without assistance), and able to advance each leg independently ≥3 steps. Individuals with progressive spinal lesions, history of uncontrolled cardiovascular irregularities, altered cognitive status, orthopedic pathology, intracranial metal, or history of seizures were excluded from the study.

4.2.3 Motor Skill Training (MST) Intervention

Details of the MST rationale and training parameters are included in the primary study publication (Evans & Field-Fote, 2022). Briefly, the MST intervention consisted of six exercises performed as a circuit (60 seconds/exercise, 4 total circuits). Participants were encouraged to complete each exercise as quickly as possible to promote rapid activation/deactivation of targeted muscle groups and to ensure at least moderate exercise intensity (i.e., ≥40% heart rate reserve) was achieved. Training intensity thresholds were calculated for each participant from resting and peak heart rates obtained during baseline administration of an upper body cycle (881E Monark Ergometer) graded-exercise test. The

average time to complete the MST circuit was 37±6.1 minutes, including transition time between exercises.

4.2.4 Walking Outcomes

Three 10-meter walk test (10MWT) trials were completed at each time point with two minutes of seated rest between walks. At the start of each trial, instructions were given to "*walk as quickly and safely as possible*". Assistive walking devices were permitted and kept consistent throughout the study. Walking speed (WS; m/min) was calculated from the distance divided by the total time to complete the walk. The average WS of three walks was used in the analyses.

Step length (STL; m), for both stronger and weaker limbs, and step frequency (SF; steps/min) were collected from a pressure sensitive instrumented walkway (GAITRite, CIR Systems Inc., NJ, USA). Stronger and weaker limbs were determined from baseline lower extremity motor scores obtained from clinical examination. The average STL and SF across three walk trials was calculated. To account for interindividual differences in lower limb lengths (Bogen et al., 2018; Murakami & Otaka, 2017; Rota et al., 2011), STL and SF were adjusted for body height. Prior to analyses, STL and SF were normalized using the following equations:

- STL=(step length/participant body height)x(mean sample body height)
- SF=(step frequency)x(participant body height/mean sample body height)$^{1/2}$

The walk ratio (WR; m/steps/min) was calculated as the ratio of normalized STL to SF (WR=STL/SF).

4.2.5 Data Analysis and Statistics

Data were managed in Microsoft Excel and analyses performed in SPSS v28 (IBM, 2020). Descriptive statistics were generated at each time point, with normality plots and Shapiro Wilks tests examined for distributional abnormalities. Given strength differences between limbs are common among PwMISCI and may manifest in differences in STLs, stronger and weaker STL were compared at each time point using paired-samples *t*-tests. In the absence of significant between-limb differences ($p < 0.05$), STLs from both limbs were averaged and used to calculate a single WR value (Ducharme et al., 2018). Cumulative absolute change in outcomes was calculated as the mean difference between measures at baseline (D1) and 24-hours post-intervention (D5). Relative change was calculated as both the ratio and % change in outcomes from D1 relative to each subsequent time point (D2, D3, D4, D5).

Differences in outcomes may be attributable to differences in WS; therefore, the full sample was divided into two groups (slow and fast walkers) according to the baseline walking speed threshold of 41.4m/min (0.69m/s). This cut-off was selected based on the minimum threshold walking speed among persons with chronic SCI that classifies individuals as independent community ambulators (van Hedel & Group, 2009). Following slow versus fast designation, within-group change in outcomes was analyzed using paired-samples *t*-tests. Between-groups differences were examined using independent samples *t*-

tests. Relationships between change in walking outcomes were examined using Pearson product-moment correlation analyses and calculated from the difference in each outcome from D1-D2, D2-D3, D3-D4, and D4-D5. Results are reported as the correlation coefficient (r) along with 95% confidence interval. In the case of non-normally distributed data, Spearman's rank-order correlations (r_s) were calculated. Strength of relationships between variables were defined as weak ($r \leq 0.39$), moderate ($r = 0.40\text{-}0.69$), or strong ($r > 0.69$).(Schober et al., 2018) Finally, simple linear regression analysis was performed to examine individual contributions of ΔSF and ΔSTL to ΔWR. The level of significance for all analyses was set at $p < 0.05$.

4.3 Results

Twenty-six individuals were enrolled in the study. One participant withdrew after baseline testing. Data from the remaining participants (19M/7F) were included in the analyses. Mean age and time since injury of the full sample was 48.4 years and 86.7 months, respectively. Eighty-eight % (22/25) of participants presented with tetraplegia and 92% (23/25) were classified as AIS-D. Participant demographics and baseline clinical characteristics are provided in Table 4.1.

No differences between stronger and weaker height-normalized STL were observed at any time point (D1: $p = 0.079$; D2: $p = 0.417$; D3: $p = 0.701$; D4: $p = 0.335$; D5: $p = 0.413$); therefore, STL was calculated from the average of both limbs, and the WR was subsequently calculated from the combined-limb average for each participant. Subgroup stratification according to baseline walking speed resulted in designation of 15 participants

as slow walkers and 10 participants as fast walkers. The relationship between WR and WS across all time points among slow versus fast walkers is depicted in Figure 4.1. Visual inspection of histograms and Shapiro Wilk's test indicated normally distributed data for all outcomes, with the exception of the WR among the full sample; therefore, median values for this variable were included and the absolute ΔWR was examined using Wilcoxon Signed-Ranks tests.

Table 4.1. Baseline demographics and clinical characteristics for the full study sample and according to baseline walk speed stratification.

Characteristics	Full Sample (n=25)	Slow Walkers (n=15)	Fast Walkers (n=10)
Age, y	48.4 (13.2)	50.0 (12.9)	45.9 (13.8)
Sex, male/female	18 / 7	11 / 4	7 / 3
Body height, m	1.79 (0.09)	1.79 (0.09)	1.78 (0.09)
BMI, kg/m^2	24.5 (5.4)	23.8 (4.6)	25.5 (6.5)
Time since injury, mo	86.7 (87.2)	107.7 (95.0)	55.3 (66.4)
NLI category	Cervical = 22 / Thoracic = 3	Cervical = 13 / Thoracic = 2	Cervical = 9 / Thoracic = 1
AIS classification	C = 2 / D = 23	C = 1 / D = 14	C = 1 / D = 9
ISNCSCI LEMS, total score	38.9 (8.9)	35.1 (8.0)	44.5 (7.3)
GXT HR_{peak}, bpm	131.0 (21.6)	127.0 (15.2)	136.9 (28.6)
Walking speed, m/min	41.3 (30.6)	20.8 (11.0)	72.0 (23.7)
Assistive walking device use	Yes = 17 / No = 8	Yes = 14 / No = 1	Yes = 3 / No = 7

Abbreviations: NLI, *neurological level of injury*; AIS, *American Spinal Injury Association Impairment Scale*; ISNCSCI, *International Standards for Neurological Classification of Spinal Cord Injury*; LEMS, *lower extremity motor score*; GXT, *graded exercise test*; HR_{peak}, *peak heart rate*; bpm, *beats per minute*. Continuous variables reported as mean (standard deviation). Categorical variables reported as counts.

4.3.1 Walking Speed (WS)

A significant increase in WS (ΔM=7.7m/min, $t(24)=5.06$, $p<0.001$) was observed for the full sample from D1 to D5. Naturally, baseline WS was higher among fast (M=71.9m/min) versus slow (M=20.1m/min) walkers. Increases in WS were observed for both fast (ΔM=9.0m/min; $t(9)=3.09$, $p=0.013$) and slow (ΔM=6.9m/min; $t(14)=4.04$, $p=0.001$) walkers from D1 to D5. Relative change in WS among slow walkers (1.46, ↑46%) was nearly three times higher than fast walkers (1.16, ↑16%). Absolute change between groups was not significant, $t(23)=-0.67$, $p=0.509$ (Figure 4.2). Walking speed at each time point is reported in Table 4.2.

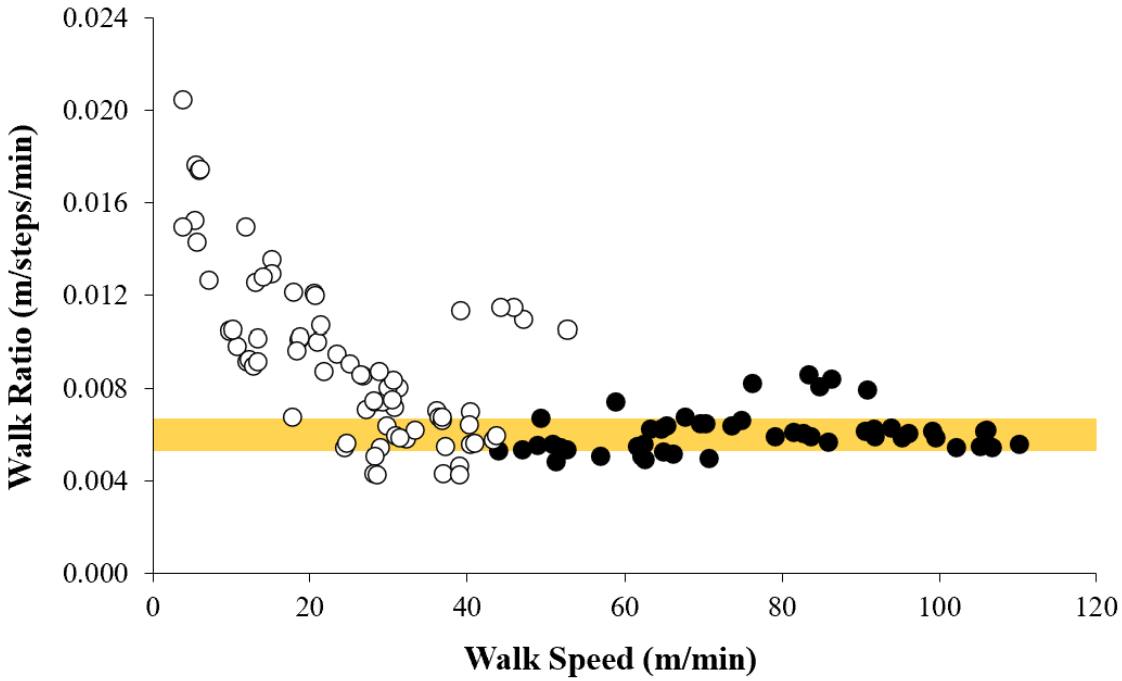


Figure 4.1. Relationship between walking speed and the walk ratio among the full study sample and subdivided into slow walkers (open circles) and fast walkers (closed circles). Data depicts outcomes collected across all time points over five consecutive days. Yellow horizontal bar reflects walk ratio range reported in non-injured adults.

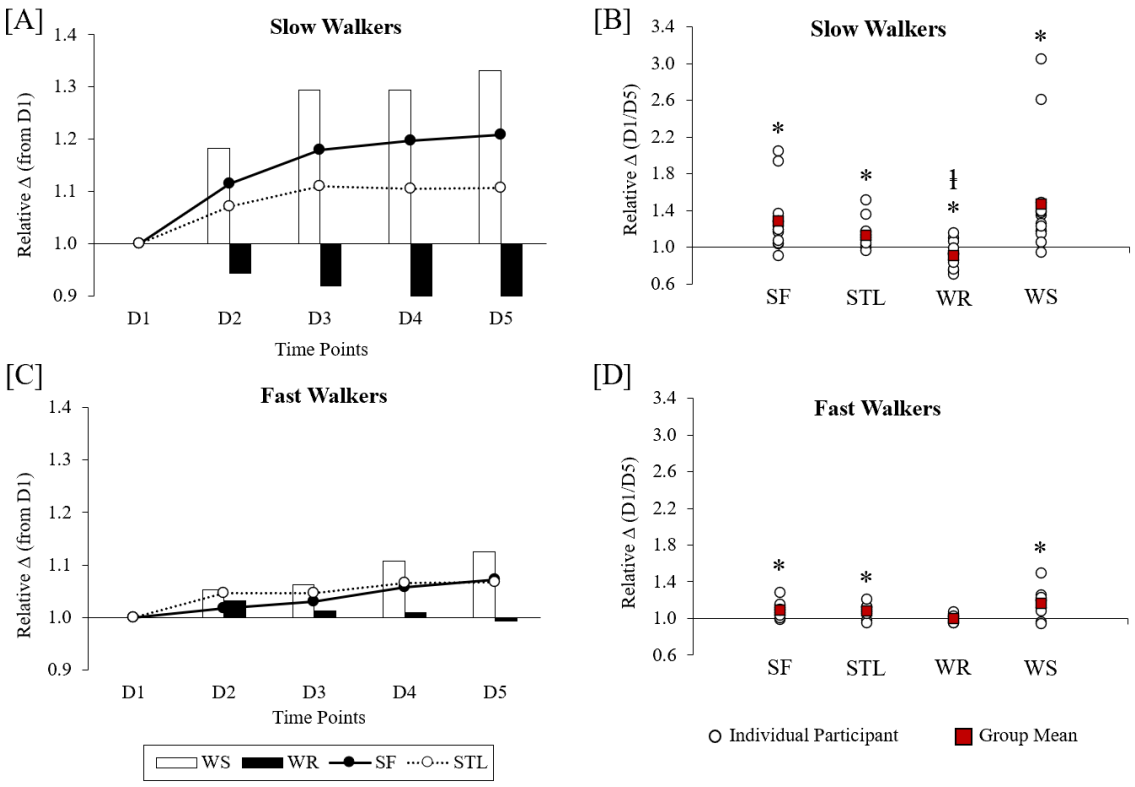


Figure 4.2. [A] and [C] depict relative change in walking outcomes from baseline to subsequent time points among slow and fast walkers, respectively. [B] and [D] depict relative cumulative change in walking outcomes from D1 to D5 among individual participants (open circles) within the slow and fast walker sub-groups, respectively. Red closed squares indicate relative group mean change for each outcome. *Significant within-group difference in the absolute change (p<0.05) from D1 to D5, paired-samples t-test. ŧSignificant between-groups difference in absolute change (p<0.05) from D1 to D5, independent-samples t-test. Abbreviations: D1, *Day 1 – baseline*; D2, *Day 2*; D3, *Day 3*; D4, *Day 4*; D5, *Day 5 – 24 hours post-intervention*; WS, *walking speed*; WR, *walk ratio*; SF, *step frequency*; STL, *step length*.

4.3.2 Step Frequency (SF) and Step Length (STL)

Significant increases in SF (ΔM=9.2steps/min; t(24)=5.13, p<0.001) and STL (ΔM=0.05m; t(24)=4.99, p<0.001) were observed among the full sample from D1 to D5. Relative change in SF (1.20, ↑20%) was twice that of STL (1.10, ↑10%). Step frequency increased from D1 to D5 among slow (ΔM=10.1steps/min; t(14)=3.92, p=0.002) and fast

(ΔM=7.8steps/min; $t(9)=3.34$, $p=0.009$) walkers. Relative change in SF was approximately three times higher among slow (1.28, ↑28%) versus fast (1.08, ↑8%) walkers. Between-groups differences in absolute change in SF was not significant, $t(23)=0.62$, $p=0.539$. Increases in STL were observed from D1 to D5 among slow (ΔM=0.04m; $t(14)=3.78$, $p=0.002$) and fast (ΔM=0.04m; $t(9)=3.13$, $p=0.012$) walkers; however, relative (slow walkers=1.12, ↑12%; fast walkers=1.08, ↑8%) and absolute change from D1 to D5 were comparable between groups, $t(23)=-0.04$, $p=0.486$ (Figure 4.2). Spatiotemporal outcomes at each time point are reported in Table 4.2.

4.3.3 Walk Ratio (WR)

The mean[median] WR at D5 (0.0076[0.0064]m/steps/min) was lower than D1 (0.0084[0.0068]m/steps/min), $Z=-2.36$, $p=0.018$, among the full sample. The WR among slow walkers decreased from D1 to D5 (ΔM=-0.0013m/steps/min; $t(14)=-2.76$, $p=0.015$); however, there was no change among fast walkers (ΔM=0.0000m/steps/min; $t(9)=-0.26$, $p=0.798$). Absolute change in the WR from D1 to D5 differed between groups, $t(14.8)=-2.67$, $p=0.018$. Relative change in the WR among slow walkers was 0.90 (↓10%). Individual participant and group mean data for the WR across time points is depicted in Figure 4.3A and 3C. Relative change in the WR among slow and fast walkers is depicted in Figure 4.2.

Table 4.2. Walking outcomes obtained over five consecutive days (intervention period from D2 – D4) among the full sample [A] and subdivided according to slow walkers [B] and fast walkers [C]. Data reported as mean (standard deviation). Significance derived from paired-samples t-test, with the exception of ΔWR for the full sample [A], which includes the median (Md) and significance derived from Wilcoxon Signed-Ranks test.

Walking Outcomes	Time Points					ΔD1–D5	D1/D5 Ratio (Δ%)
	D1	D2	D3	D4	D5		
[A] Full Sample (n=25)							
WS (m/min)	41.2 (30.6)	45.1 (29.8)	46.7 (28.9)	48.0 (29.9)	49.0 (30.6)	**7.7** (7.6) *p*<0.001	1.34 (34%)
SF (steps/min)	72.5 (35.6)	76.6 (33.9)	79.0 (33.3)	80.7 (33.7)	81.7 (34.2)	**9.2** (8.9) *p*<0.001	1.20 (20%)
STL (m)	0.50 (0.16)	0.53 (0.16)	0.54 (0.15)	0.55 (0.16)	0.55 (0.16)	**0.05** (0.05) *p*<0.001	1.10 (10%)
WR (m/steps/min)	0.0084 (0.0039)	0.0081 (0.0033)	0.0079 (0.0032)	0.0077 (0.0030)	0.0076 (0.0027)	**-0.0008** (0.0015) *p*=0.017	0.94 (-6%)
	Md=0.0068	Md=0.0072	Md=0.0067	Md=0.0067	Md=0.0064	**Md=-0.0004** *p*=0.018	
[B] Slow Walkers (n=15)							
WS (m/min)	20.1 (11.0)	24.6 (12.0)	26.9 (12.9)	26.9 (12.1)	27.7 (13.4)	**6.9** (6.6) *p*=0.001	1.46 (46%)
SF (steps/min)	48.6 (21.2)	54.2 (21.9)	57.4 (22.9)	58.2 (22.1)	58.8 (22.5)	**10.1** (10.0) *p*=0.002	1.28 (28%)
SL (m)	0.41 (0.10)	0.44 (0.10)	0.45 (0.10)	0.45 (0.10)	0.45 (0.11)	**0.04** (0.05) *p*=0.002	1.12 (12%)
WR (m/steps/min)	0.0099 (0.0043)	0.0094 (0.0037)	0.0091 (0.0036)	0.0088 (0.0034)	0.0086 (0.0030)	**-0.0013** (0.0018) *p*=0.015	0.90 (-10%)
[C] Fast Walkers (n=10)							
WS (m/min)	71.9 (23.7)	75.7 (20.0)	76.5 (18.3)	79.7 (17.2)	80.9 (18.2)	**9.0** (9.2) *p*=0.013	1.16 (16%)
SF (steps/min)	108.2 (17.8)	110.1 (15.4)	111.5 (13.3)	114.4 (13.0)	116.0 (12.2)	**7.8** (7.4) *p*=0.009	1.08 (8%)
SL (m)	0.65 (0.12)	0.68 (0.11)	0.68 (0.10)	0.69 (0.10)	0.69 (0.10)	**0.04** (0.05) *p*=0.012	1.08 (8%)
WR (m/steps/min)	0.0060 (0.0010)	0.0062 (0.0011)	0.0061 (0.0009)	0.0061 (0.0010)	0.0060 (0.0009)	0.0000 (0.0002) *p*=0.798	1.00 (0%)

Abbreviations: D1, *Day 1 - baseline*; D2, *Day 2*; D3, *Day 3*; D4, *Day 4*; D5, *Day 5 - 24 hours post-intervention*; WS, *walking speed*; SF, *step frequency*; STL; *step length*; WR, *walk ratio*.

4.3.4 Relationships Among Walking Outcomes

A strong positive relationship was observed between ΔSF and ΔWS among the full sample, $r(98)=0.83$, $p<0.001$, as well as slow, $r(60)=0.91$, $p<0.001$, and fast walkers, $r(40)=0.82$, $p<0.001$. Likewise, there was a strong positive relationship between ΔSTL and ΔWS among the full sample, $r(98)=0.82$, $p<0.001$, slow walkers, $r(60)=0.81$, $p<0.001$, and fast walkers, $r(40)=0.84$, $p<0.001$. Change in the WR was unrelated to ΔWS among the full sample, $r_s(98)=-0.25$, $p=0.806$, and fast walkers, $r(40)=0.17$, $p=0.300$; however, there was a weak but significant inverse association between ΔWR and ΔWS among slow walkers, $r(60)=-0.27$, $p=0.036$.

Among fast walkers, ΔSF was inversely associated with ΔWR, $r(40)=-0.38$, $p=0.015$, while ΔSTL was positively associated with ΔWR, $r(40)=0.65$, $p<0.001$ (Figure 4.3D). Similarly, among slow walkers there was an inverse association between ΔSF and ΔWR, $r(60)=-0.51$, $p<0.001$; however, ΔSTL was not associated with ΔWR, $r(60)=0.08$, $p=0.548$ (Figure 4.3B). Data from correlation analyses are reported in Table 4.3.

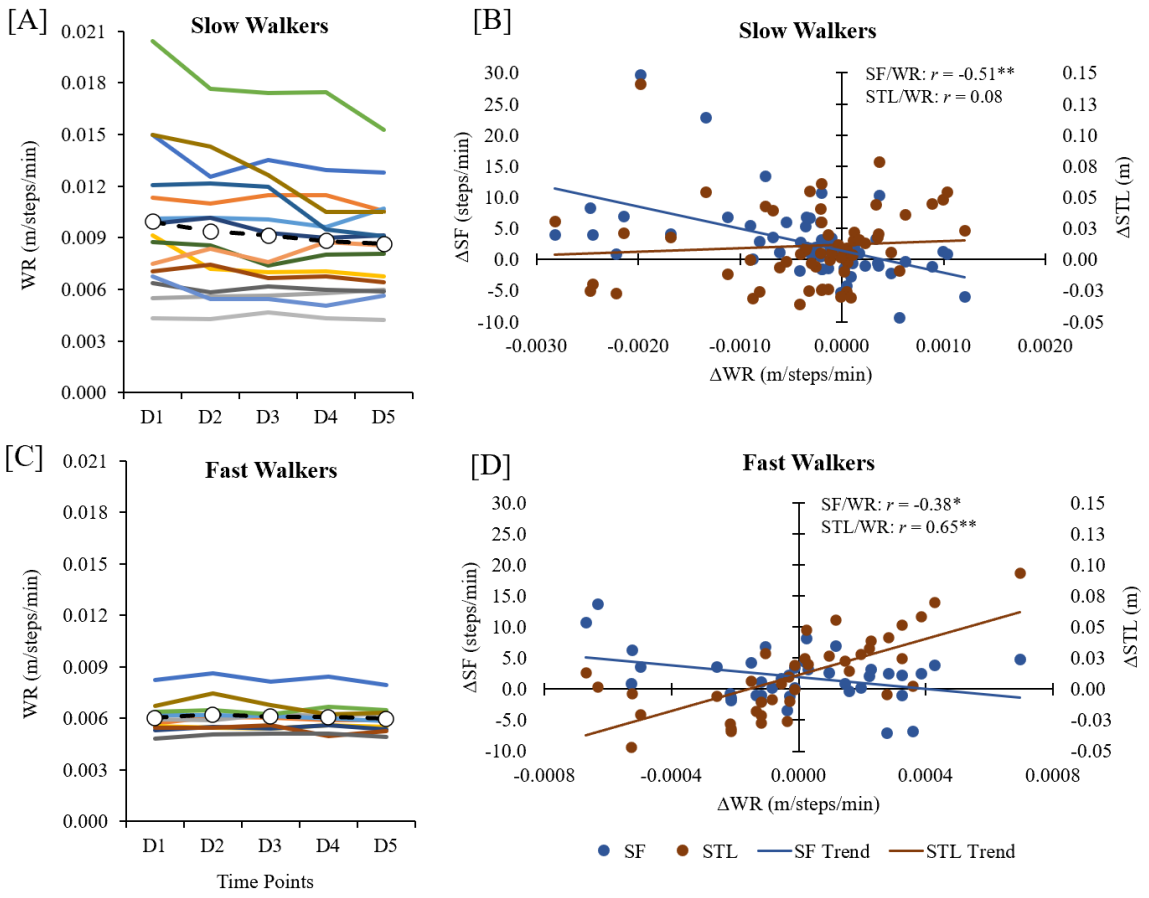


Figure 4.3. [A] and [C] depict individual participant (colored lines) and group mean (hashed black line with open circles) data for the WR over five consecutive days among slow and fast walkers, respectively. [B] and [D] depict relationships between the absolute day-to-day change in SF, STL, and the WR among slow and fast walkers, respectively. Red trend lines and circles represent the relationship between ΔSTL and ΔWR. Blue trend lines and circles represent the relationship between ΔSF and ΔWR. Pearson correlation coefficients (r) for each group are inset on the respective figures. Slow Walkers: **Significant negative correlation between ΔSF and ΔWR, $p<0.01$. No relationship was observed between ΔSTL and ΔWR, $p=0.49$. Fast Walkers: **Significant positive correlation between ΔSL and ΔWR, $p<0.01$. *Significant negative correlation between ΔSF and ΔWR, $p<0.05$. Abbreviations: D1, *Day 1 – baseline*; D2, *Day 2*; D3, *Day 3*; D4, *Day 4*; D5, *Day 5 – 24 hours post-intervention*; WR, *walk ratio*; SF, *step frequency*; STL, *step length.*

Table 4.3. Relationship among absolute change in walking outcomes over five consecutive days.

Walking Outcomes	Δ WS	Δ WR	Δ SF	Δ SL
[A] Full Sample				
Δ WS	1.00			
Δ WR	-0.03 (-0.23 – 0.18)	1.00		
Δ SF	0.83** (0.76 – 0.88)	-0.45** (-0.60 – -0.27)	1.00	
Δ SL	0.82** (0.74 – 0.87)	0.38** (0.19 – 0.54)	0.56** (0.41 – 0.68)	1.00
[B] Slow Walkers				
Δ WS	1.00			
Δ WR	-0.27* (-0.49 – -0.02)	1.00		
Δ SF	0.91** (0.85 – 0.94)	-0.51** (-0.68 – -0.29)	1.00	
Δ SL	0.81** (0.70 – 0.88)	0.08 (-0.18 – 0.33)	0.64** (0.46 – 0.77)	1.00
[C] Fast Walkers				
Δ WS	1.00			
Δ WR	0.17 (-0.15 – 0.46)	1.00		
Δ SF	0.82** (0.68 – 0.90)	-0.38* (-0.62 – -0.08)	1.00	
Δ SL	0.84** (0.72 – 0.91)	0.65** (0.43 – 0.80)	0.42* (0.12 – 0.65)	1.00

Note: Values reported as Pearson correlation coefficient (r) (95% CI), with the exception of Full Sample correlations between change in walking outcomes and ΔWR, which are reported as Spearman's correlation coefficient (r_s) (95% CI). *p<0.05. **p<0.01.

The fitted linear regression model for ΔSF among slow walkers was: ΔWR=0.0000-0.00007*ΔSF. The overall regression was statistically significant, R^2=0.26, F(1,58)=20.39, p<0.001, indicating 26% of the variability observed in ΔWR could be

explained by ΔSF. Change in STL did not contribute to ΔWR among slow walkers, R^2=0.01, F(1,58)=0.36, p=0.548. Among fast walkers, the fitted regression model for ΔSF was: ΔWR=0.00004-0.00003*ΔSF. The overall regression was statistically significant, R^2=0.15, F(1,38)=6.45, p=0.015. The fitted regression model for ΔSTL (ΔWR=-0.00008+0.006*ΔSTL) was also significant, R^2=0.43, F(1,38)=28.42, p<0.001. Among fast walkers, ΔSTL accounted for more than twice the observed ΔWR (43%) compared to ΔSF (15%).

4.4 Discussion

In the present study, we examined the relationship between STL and SF, as quantified by the WR, during overground walking among PwMISCI. Additionally, we investigated the effects of high-velocity MST on changes in walking outcomes and STL-SF coordination. We highlight three important findings from the study. First, in contrast to previous reports in other neurological populations (Ambrus, Sanchez-Miguel, et al., 2019; Kalron, 2016; Rota et al., 2011; Suzuki et al., 1999), the WR among our full sample was higher than non-injured adults (Bogen et al., 2018; Murakami & Otaka, 2017; Sekiya & Nagasaki, 1998) suggesting the WR may be sensitive to capturing the unique constraints imposed by SCI on the ability to coordinate the magnitude and rate of lower limb movements during walking. Second, while on the whole the WR was higher among the full sample, subgroup analyses revealed WR values among fast walkers that were comparable to non-injured adults. Furthermore, the WR constancy (Murakami & Otaka, 2017) was preserved among fast walkers, indicating the ability to coordinate STL and SF at higher

walking speeds (>41.4 m/min) is conserved among this subset of participants. Finally, in contrast to fast walkers, slow walkers demonstrated greater variability in the WR with higher values associated with slower WS. Finally, in contrast to fast walkers, slow walkers demonstrated greater variability in the WR with higher values associated with slower WS. While this may reflect a diminished capacity to balance increases in STL with increases in SF, three days of MST was associated with increases in WS that coincided with a decrease in the WR approaching non-injured values. This decrease was mediated primarily through an effect on SF. This observation may point to a specific mechanism by which high-velocity MST facilitates improvements in overground WS among PwMISCI with greater mobility deficits.

Walking speed provides a meaningful measure of functional mobility, while the WR provides an account of the spatiotemporal coordination underlying WS modulation. Previous findings among persons with Parkinson disease (Ambrus, Sanchez-Miguel, et al., 2019), multiple sclerosis (Kalron, 2016; Rota et al., 2011), and stroke (Suzuki et al., 1999) have reported WR values that are 13-50% lower than non-injured adults (Bogen et al., 2018; Murakami & Otaka, 2017; Sekiya & Nagasaki, 1998). This can be attributed to walking strategies that involve shorter and more frequent steps, which serves to decrease the muscular work required to manage step-to-step accelerations of the body's mass and to improve stability by increasing double limb support time (Beyaert et al., 2015). In contrast, the WR among the full sample of participants in our study was 22-26% higher than previous reports among non-injured individuals. These contrasting results suggest the WR is sensitive to discriminating between spatiotemporal coordination strategies used by persons with differing underlying neuropathology. For instance, Parkinsonian gait is

characterized by deficits in the internal regulation of STL while the control of SF remains intact (Morris et al., 1994; Morris et al., 1996). In persons with multiple sclerosis, decreased WS is associated with a decrease in STL and an increase in double support time (Coca-Tapia et al., 2021). Finally, individuals post-stroke exhibit SFs equal to or higher than non-injured counterparts, while STLs are generally lower (Jonsdottir et al., 2009). In contrast, PwMISCI demonstrate a diminished capacity to generate high SFs, while generally retaining the ability to modulate STL (Pepin et al., 2003).

While differences in STL-SF coordination among different neurological populations might account for the higher WR observed among our participants with SCI, this only held true among slow walkers. The WR constancy was preserved among fast walkers, indicating the ability to modulate both STL and SF at higher walking speeds was conserved among this subset of participants. Conversely, slow walkers demonstrated greater variability in the WR with higher values associated with slower WS. Taken as a whole, not only does the WR appear to discriminate among individuals with differing neuropathology but also between individuals with similar neurological condition but differing degrees of function. Beyond WS, SF, or STL alone, the WR may provide additional insights into the spatiotemporal coordination strategies employed by PwMISCI, particularly among those with greater motor deficits.

We anticipated that the MST circuit would lead to increases in the ability to generate higher SFs as reflected in a lower WR, in so far as STL modulation remained intact. Participation in high-velocity MST was associated with increases in overground WS regardless of being categorized as slow or fast walkers; however, the relative change was nearly three times higher among slow (↑45%) versus fast walkers (↑16%). This may be

explained in part by between-groups differences in baseline WS. For instance, individuals with slower baseline WS may have a greater capacity for change, and small absolute changes may appear as large relative effects. In contrast, individuals with faster baseline WS may already be near peak walking capacity, and while additional improvements may still be possible, much greater absolute changes are needed to produce large relative effects. Notwithstanding these possibilities, increases in WS were correlated with increases in both SF and STL among slow and fast walkers, indicating SF and STL modulation contributed to improvements in overground walking performance following MST, regardless of baseline walking capacity. However, an important between-groups distinction was the divergent contributions of these spatiotemporal parameters to changes in WS, as reflected in the WR.

The overall decrease in the WR among the full sample was almost entirely attributable to changes that occurred among slow walkers (ΔWR=-0.0012m/steps/min), with increases in SF, but not STL, contributing to the change. This indicates SF modulation was the predominating characteristic influencing changes in the WR among this group. In contrast, among fast walkers, the WR remained constant with increases in WS, indicating STL-SF coordination was preserved among these individuals. While both STL and SF manipulations can lead to increases in WS, these results clearly show that PwMISCI with differing levels of impairment employ different spatiotemporal coordination strategies to accomplish the same outcome (i.e., faster walking). This observation establishes the importance of evaluating STL and SF in terms of their interaction, as opposed to evaluating each parameter independently. Furthermore, information revealed by the WR could help

inform the effectiveness of motor training interventions aimed at targeting the unique deficits experienced by PwMISCI.

The magnitude of change in SF (Δ=10.1steps/min) achieved by slow walkers exceeded prior locomotor training studies involving much longer durations and comparable group-level baseline WS. For example, 36 sessions of bodyweight-supported treadmill training resulted in an increase in SF of 9.0steps/min (Leech et al., 2016). In a study comparing ≈50 sessions of one of four locomotor training interventions, increases in SF ranged from 1.5-5.0steps/min, depending on the approach (Nooijen et al., 2009). In a small case series, 30 sessions of combined plyometric and resistance training resulted in a mean increase in SF of 4.1steps/min (Gregory et al., 2007). Incidentally, after extracting available pre-post data from two of the three studies above (Gregory et al., 2007; Leech et al., 2016), an estimate of the WR was calculated. In both cases, WR values increased following treadmill and plyometric/resistance training, with greater relative change in STL compared to SF. This finding contrasts our results among slow walkers and may be explained by differences in the motor training approaches employed.

We note two important distinctions between our MST circuit and prior motor training interventions. First, evidence in non-injured adults indicates the spatiotemporal interactions used to modulate walking speed on a treadmill may differ from those employed overground. For example, treadmill walking constrains movement variability and impedes the temporal stepping rhythm, which overemphasizes the need to modulate STL to maintain a given walking speed (Dal et al., 2010; Hollman et al., 2016). Second, the use of bodyweight-supported systems leads to a diminution in peak ground reaction forces and a reduction in the propulsive impulse generated during walking (Apte et al., 2018) and

plyometric exercise (Elias et al., 2015). With the exception of one exercise, our intervention emphasized rapid lower limb movements performed under full weight-bearing conditions. It is widely accepted that motor unit recruitment varies depending on the mechanical load and the speed and type of muscle contraction produced (Duchateau et al., 2006; Van Cutsem et al., 1998). For example, rapid ballistic contractions of the tibialis anterior involving high rates of torque development require approximately three times the motor unit recruitment to produce a given force compared to slow-ramp contractions (Desmedt & Godaux, 1977). Additionally, the magnitude of neural drive is dependent on the target force, such that exposure to lower forces requires recruitment of fewer motor units, unless the speed of contraction is increased (Aeles et al., 2022). Consequently, the specificity and demands of our training approach (i.e., high-velocity movement under full bodyweight) may have created a more favorable environment for facilitating enhanced motor unit recruitment and higher rates of force development. This, in turn, may have translated to greater ability, particularly among slow walkers, to generate higher SFs during overground walking, resulting in a lower WR. Further investigation is needed to determine whether prolonged high-velocity motor training will produce consistent and lasting change in spatiotemporal coordination in PwMISCI.

4.5 Study Limitations

Height-normalized spatiotemporal data is inconsistently reported in the SCI literature and differences in the conditions under which walking outcomes were collected (i.e., overground vs. treadmill) limits direct comparisons between our findings and prior

studies. While the total number of participants enrolled in the study is comparable to or exceeds many locomotor training studies involving PwMISCI, the smaller number of fast compared to slow walkers decreases the statistical power and diminishes the strength of interpretation of between-groups differences. Future studies comparing high-velocity MST to other locomotor training approaches would benefit from *a priori* stratification between slow and fast walkers in order to ensure equal representation of participants with differing walking capacities.

4.6 Conclusions

In the present study, we characterized the relationship between spatiotemporal parameters subserving WS (i.e., STL and SF) and the coordination of these parameters (i.e., WR) during overground walking and following MST. The WR appears sensitive to discriminating between individuals with differing neuropathology and degrees of walking function utilizing different spatiotemporal control strategies during ambulation. Additionally, three days of MST was associated with increases in WS among slow walkers that coincided with decreases in the WR. This decrease was mediated primarily through an effect on SF, which may point to a specific mechanism by which high-velocity training facilitates improvements in overground WS. Further investigation involving longer training durations will reveal whether cumulative effects of prolonged high-velocity MST can produce lasting change in spatiotemporal coordination and walking performance in PwMISCI.

CHAPTER 5. CONCLUSIONS AND FUTURE WORK

5.1 Conclusions and implications

Recovery of motor function, including walking and upright balance, is central to rehabilitation for PwMISCI and has implications for long-term health and independence following injury. Critical considerations of ongoing interest are the long-term accessibility and costs associated with obtaining meaningful improvements in walking and balance function following SCI. In the present study, we examined the effectiveness of a MST circuit developed based on evidence for active volitional engagement to increase corticospinal drive and enhance motor output, intensive training to activate physiologic mechanisms that support motor skill acquisition and consolidation, and specificity of training to facilitate rapid lower limb movements and faster overground walking speeds. In addition, the intent of the MST circuit was to address limitations posed by alternative locomotor training approaches that emphasize slow, repetitive massed-practice stepping, require lengthy training periods, and involve costly equipment that limits long-term accessibility for PwMISCI once discharged from initial rehabilitation. In addition, we examined whether concurrent application of tDCS to the motor cortex and cerebellum, two supraspinal regions critical to motor control and learning, would enhance the effects of MST.

According to the findings, participation in three days of MST was associated with significant improvements in overground walking speed and distance, with changes in walking speed approaching or exceeding studies involving much longer training durations. Additionally, increases in walking speed were associated with increases in spatiotemporal

characteristics and improved spatiotemporal coordination, with changes in step frequency contributing to walking speed modulation to a greater extent than step length among individuals with greater walking deficits. This observation may point to a specific mechanism by which intensive, high-velocity MST facilitates improvements in overground walking speed, namely by enhancing one's ability to increase the rate at which they can generate steps. Given the short training duration, these observed improvements are most likely attributable to neurological (central) adaptations, as the time course of MST would not have been sufficient to induce muscular (peripheral) adaptations associated with longer periods of motor training (Folland & Williams, 2007; Hughes et al., 2018). It may be the case that the effects of MST will be further enhanced with longer training durations by facilitating Type II muscle fiber recruitment and hypertrophy, increasing muscle cross-sectional area, increasing mitochondrial density and efficiency, and/or improving agonist-antagonist neuromotor control. If both central and peripheral adaptations can be realized with prolonged training, then the MST program could be a valuable alternative and more accessible means by which individuals with limited functional capacity can achieve (or maintain) improvements in walking function beyond the clinic. Additional outcomes measures could be included in future studies to assess both the neurological and muscular adaptations associated with longer-term MST.

In addition to improvements in walking outcomes, three days of intensive MST was associated with improvements in upright balance performance and a reduction in perceived fear of falling when performing activities of daily living in the home and community. Muscle weakness, impaired balance, and concern for falling contribute to a higher frequency of falls among individuals with SCI who are ambulatory (Jorgensen et al., 2017;

Kahn et al., 2019), and enhanced balance performance is associated with improved walking ability, reduced falls incidence, and enhanced confidence in performing activities of daily living (Datta et al., 2009; Forrest et al., 2012; Singh et al., 2021). Our finding that MST was associated with improvements in measures of balance function is consistent with longer-term motor training interventions reported in PwMISCI (Houston et al., 2020; Morrison et al., 2018; Neville et al., 2019; Stevens et al., 2015); however, it is unclear whether improvements in balance performance were the result of a decrease in fear of falling or if a reduced fear of falling contributed to improved balance performance. Further examination into the relationship between qualitative measures related to movement confidence and fear of falling and quantitative measures associated with static and dynamic balance performance would be of value. Regardless of the interactions between these measures, given the effects of the three-day training intervention are comparable to longer training studies and that the design of the MST circuit is intended to be accessible across a range of settings, findings from this pilot study provide evidence supporting the value of further investigation into the long-term feasibility and potential benefits of the MST program for improving balance function.

While, according to our selected outcome measures, no additive effects of tDCS were observed, it is possible that the specificity of effects of combined MST and tDCS were not reflected in the general walking and balance measures assessed in the present study. Prior literature describes tDCS-enhancing effects when stimulation is paired with specific lower extremity motor tasks such as ankle dorsi-/plantar-flexion control during visuomotor tracking (Sriraman et al., 2014), quadriceps activation during seated knee extension (Washabaugh et al., 2016), and single-leg standing balance with visual feedback

(Andani et al., 2020). The role of the cerebellum in balance and postural control is well documented. It may be the case that application of tDCS using the M1-cerebellar montage we employed resulted in an effect on specific aspects of motor function that were not reflected in our general measures of functional performance. For example, although overall changes in BBS scores were comparable between those who received active- versus sham-tDCS, upon closer examination of the 14 individual tasks within the BBS, significant between-groups differences were observed for the balance task that directly replicated exercise #2 of the MST circuit (i.e., step taps; see Appendix C.1 and C.2). While the polarity-specific effects of cerebellar-tDCS on motor behavior are equivocal (Oldarti & Schutter, 2018), inhibitory (cathodal) tDCS to the cerebellum enhances motor cortical excitability (Kaski et al., 2012), presumably through disinhibition of the dentate-thalamo-cortical pathway (Behrangrad et al., 2019; Galea et al., 2009), and is associated with improved balance performance in neurologically intact adults (Andani et al., 2020). Collectively, these observations may indicate that the effects of the tDCS electrode montage we used are highly task specific and do not necessarily translate to alternative motor tasks not directly replicated during the delivering of stimulation (i.e., level overground walking).

The cerebellum plays an important role in monitoring and modifying ongoing locomotor activity according to sensory information derived from activity of spinal CPGs and position of lower limb segments (Grillner & El Manira, 2020). Cerebellar contributions to locomotor control are most evident in cases where perturbations or obstacles are encountered in the environment (Andersson & Armstrong, 1987). Prior research has demonstrated greater improvements in standing balance performance in response to

perturbation following delivery of cerebellar tDCS (Andani et al., 2020; Kaski et al., 2013; Kaski et al., 2012); however, the influence of cerebellar tDCS on balance or limb trajectory corrections during stepping has yet to be characterized. Moreover, the cerebellum is capable of undergoing neuroplastic changes that contribute to motor learning (Hull, 2020), primarily through integration of coupled afferent inputs leading to long-term depression of Purkinje cell spike activity (Hirano, 2013). Cathodal-cerebellar tDCS reduces the average firing rate of Purkinje cells (Zhang et al., 2021), and cerebellar inhibition induced by TMS enhances motor cortical plasticity (Popa et al., 2013). Cathodal-tDCS combined with sensory feedback improves retention of a standing balance task (Andani et al., 2020), while excitatory anodal-cerebellar tDCS diminishes the rate of learning during a lower limb force-feedback test (Dutta et al., 2014). It is possible that the M1-cerebellar tDCS montage we employed had immediate and/or persistent effects on aspects of locomotor function that were not uncovered by the specific outcome measures and methodology we employed.

For example, capturing kinematic measures of alterations in lower limb coordination, limb segment trajectories, or center of mass adjustments in response to environmental perturbations during stepping (e.g., stepping over obstacles, walking over uneven terrain) may reveal unique contributions of M1-cerebellar tDCS not captured during constant velocity, level ground walking. Furthermore, including multiple within-day and/or post-intervention testing intervals may reveal differences in motor skill retention and consolidation rates between those who received active- versus sham-tDCS. Further investigations are needed to determine whether the specificity of M1-cerebellar tDCS is limited in its ability to influence level ground walking, whether the effects of this montage would be greater during perturbed walking where cerebellar contributions may be

greater, or whether the lack of findings of tDCS are simply due to other methodological factors not addressed by the current study design. Answers to these questions may have implications for how and in what way tDCS would need to be administered in clinical and community-based settings in order to enhance relevant motor outcomes.

5.2 Suggestions for future work

Despite being the largest available study of intensive, high-velocity lower extremity motor training to improve walking and balance outcomes in PwMISCI and the largest study of tDCS to augment lower extremity function in this population, several methodological limitations are considered here and may guide future research investigating the specific interventions employed. First, due to limited access to participants under COVID-19 restrictions, study enrollment was 5 participants short, and our recruitment goal of 30 participants (15 per group) was not reached leaving group-level sample sizes unbalanced. This may have led to the study being underpowered, and it is possible we failed to detect an additive effect of tDCS when in fact an effect was present. It should be noted, however, that in pilot studies, statistical modelling suggests a sample size of 12 participants per group is sufficient for estimating mean change and variability in outcomes (Julious, 2005). Moreover, given the similarity in the magnitude of within-groups change in outcomes, even if statistically significant between-groups differences were detected, it is doubtful that the magnitude of these differences would have been clinically meaningful, and the inclusion of 5 additional participants would not have changed the fact that the MST circuit produced robust effects on walking and balance outcomes. Nevertheless, future studies with larger

samples and comparable group-level allocation of participants could strengthen interpretation of findings concerning the potential effectiveness of paired motor training and tDCS.

Second, differences in baseline function and clinical characteristics may contribute to differences in responsiveness to intervention. For instance, mean baseline walking speed and total LEMS differed between groups, favoring the sham-tDCS group for walking speed and the active-tDCS group for LEMS. Additionally, across the full sample, these measures were higher among our participants compared to some prior studies. Evidence indicates that lower extremity strength is associated with walking speed in PwSCI (DiPiro et al., 2015), and baseline walking speed may be a predictor of responsiveness to training (Jones et al., 2014a). We identified improvements in walking function in response to three days of MST that differed between slow and fast walkers. Generalizability and interpretability of findings for future studies may be aided by stratifying participants according to walking speed and/or degree of spared lower limb motor function at baseline. Additionally, baseline physical conditioning may influence the underlying mechanisms linking intensive exercise with enhanced motor skill acquisition and retention (i.e., upregulation of BDNF and other LTP-related compounds). Inclusion of a physical conditioning wash-in period may minimize differences in fitness status that could influence response to intensive motor training. Additionally, measuring peripheral concentrations of BDNF and other LTP-related compounds at baseline and post-intervention may be important for identifying interindividual differences in physiological biomarkers that are associated with enhanced motor skill performance and learning.

Third, between-day change contributed to overall improvements in overground walking speed to a greater extent than within-day change. Given that a significant percentage of the between-day change occurred between D1 (baseline) and D2 (1st intervention day), we cannot rule out the influence of participant expectation (i.e., the Hawthorne Effect) on walking outcomes. Additionally, twenty-two participants had at least some knee extensor spasticity considered to be mild (n=9), moderate (n=8), or severe (n=5) based on clinical measures of spasticity (i.e., SCATS). While lower extremity spasticity (i.e., intermittent or sustained involuntary muscle activation leading to spasms and limb stiffness (Pandyan et al., 2005)) may contribute to impaired motor control and gait abnormalities in PwMISCI (Krawetz & Nance, 1996), individuals with knee extensor weakness may benefit from increased spasticity-induced quadriceps stiffness during the stance phase of walking (Duffell et al., 2015). Repetitive stretch-shortening cycle exercise is associated with diminished spinal reflex sensitivity (Avela et al., 1999; Nicol et al., 1996), and unpublished observations from our study revealed within-day, but non between-day, decreases in knee extensor spasticity severity (Appendix C.3) that may have contributed to day-to-day differences in walking performance. Examining the contribution of high-velocity MST to changes in spinal reflex modulation and lower limb spasticity in PwMISCI could be a valuable addition to future studies and could reveal important underlying neurophysiological mechanisms associated with changes in walking performance following MST. Furthermore, because both participant expectation and day-to-day variability in spasticity severity may influence between-day walking outcomes, it may be necessary to include multiple baseline assessments to ensure stable measures of walking function are established prior the start of motor training.

Fourth, future studies could be improved by accounting for specific features of the MST intervention that may have contributed to changes in motor outcomes. For instance, all individuals participated in the MST circuit; therefore, the absence of a non-MST comparison group makes it difficult to discern the unique contributions of the intervention. Inclusion of an alternative exercise comparison group (e.g., lower body cycling, recumbent stepping, upper body ergometry) with matched exercise intensity could shed light on whether performance of the specific motor tasks included in the MST accounted for the observed improvements in walking and balance function or whether the exercise intensity alone was the driver of functional improvements, regardless of the tasks performed. Additionally, we emphasized high velocity, cyclic lower limb movements performed during the MST circuit, and it may be that the intensity of training is less important than the conditions under which movements are performed. Future studies could include a comparison training intervention in which the velocity and frequency of lower limb movements, as well as the intensity of exercise, are matched to the MST circuit but performed under alternative conditions (e.g., seated recumbent stepping or seated elliptical exercise). This intervention design could aid in identifying which aspects of motor training are most important for facilitating improvements in overground walking function. Moreover, while there were no differences in training durations between participants, it is possible that individuals with greater motor function completed more repetitions and were able to generate higher movement velocities during MST. Tracking these metrics over the course of a longer training period may reveal inter-individual differences in MST performance that contribute to differences in the magnitude of change in outcomes following training.

Fifth, while we failed to observe an additive effect of tDCS, numerous electrode montages and stimulation parameters have been proposed that may differentially influence the underlying neurophysiology of targeted neural structures (Nasseri et al., 2015). The size, location of the anode and cathode, and number of electrodes alters the current flow and focality of tDCS. For example, compared to a dual-electrode montage, high-definition tDCS using a ringed-array of five small electrodes provides more precise localization of current flow and may optimize the delivery of tDCS to specific targeted regions of interest (Caparelli-Daquer et al., 2012). Differences in electrode configurations may, in part, account for the heterogeneity in outcomes observed between studies involving tDCS, and our findings should be viewed within the context of the specific M1-cerebellar tDCS electrode montage we employed. With this in mind, it is possible that pairing our MST intervention with an alternative tDCS electrode montage would produce different effects on measures of walking function than those observed under the current protocol.

We anticipated, based on prior literature, that combined anodal-M1/cathodal-cerebellar tDCS would enhance motor cortical excitability and facilitate corticospinal drive to muscles of the lower extremities thereby improving walking related outcomes in PwMISCI. In the present study, inhibitory cerebellar stimulation combined with excitatory M1 stimulation may have improved task-specific standing balance performance (see Appendix C.1 and C.2) but had no effect on measures of walking speed and gait quality (e.g., inter- and intra-limb coordination), which are both influenced by cortical and cerebellar projections to spinal CPGs and lower limb motoneurons (Grillner & El Manira, 2020). It is possible the lack of effect on walking outcomes may have resulted from competition between the influences of anodal-M1 stimulation and cathodal-cerebellar

stimulation on spinal motoneurons responsible for controlling and coordinating muscles of the lower extremities.

For example, prior studies in neurologically intact individuals have demonstrated that excitatory anodal-tDCS of the cerebellum alone increases motor cortical inhibition (Galea et al., 2009) and enhances interlimb adaptation to split-belt treadmill walking (Jayaram et al., 2012). In contrast, inhibitory cathodal-tDCS alone increases motor cortical excitability (Galea et al., 2009) and diminishes interlimb adaptation during treadmill walking (Jayaram et al., 2012) while enhancing single-leg standing balance performance (Andani et al., 2020). These polarity-dependent, task-specific effects of cerebellar tDCS may point to a unique influence that different electrode montages have on underlying cerebellar circuitry and the resultant outflow of neural information via descending vestibulospinal and reticulospinal pathways. Given the diminished access to spinal motoneuron pools following SCI (Davey et al., 1999), the convergence of numerous descending inputs from preserved motor cortical and brain stem nuclei pathways (i.e., corticospinal, vestibulospinal, and reticulospinal tracts) on a limited number of available motoneurons may have confounded the potential positive influence of excitatory-M1 tDCS on volitional muscle activation and walking performance when combined with inhibitory-cerebellar tDCS. Future studies employing a cross-over design could aid in parsing out the independent influence of cathodal- versus anodal-cerebellar tDCS when combined with MST while at the same time accounting for inter-individual differences in response to tDCS that may contribute to differences in outcomes.

Finally, although we did not directly perform neurophysiological testing to examine responsiveness to tDCS, existing reports indicate the effects of tDCS can be highly variable

and dependent upon a wide range of intra- and inter-individual factors including differences in anatomical topography, cortical remapping following neurological injury, electrical impedance based on variations in skin and skull thickness, and behavioral/lifestyle factors (e.g., smoking status, caffeine and alcohol consumption, environmental stressors) (Horvath et al., 2016; Lopez-Alonso et al., 2015; Vergallito et al., 2022). Advanced neuroimaging (e.g., functional magnetic resonance imaging) and/or neurophysiological probing (e.g., transcranial magnetic stimulation) may aid in identifying the precise locations of targeted brain regions and/or identifying responders and non-responders to stimulation in order to optimize tDCS delivery and effectiveness. However, dependency on such methods may limit the accessibility and potential utility of tDCS in the clinic or community, where such technologies are rarely accessible or entirely impractical to implement. In addition to factors contributing to tDCS inter-individual variability, there may be physiological mechanisms associated with tDCS not yet fully understood (e.g., neurovascular coupling (Bahr-Hosseini & Bikson, 2021) and hemodynamic responses (Dutta, 2015)) that could further contribute to differences in responsiveness to tDCS and that should be considered as part of the rationale for future investigations examining the influence of tDCS neuromodulation on motor outcomes. Alternative methods for enhancing volitional motor output should also be considered and may be less susceptible to tDCS-related variability. For example, transcutaneous spinal stimulation (TSS) is a non-invasive neuromodulation approach that activates lumbar peripheral nerve roots (Hofstoetter et al., 2018), increases descending corticospinal outflow to muscles of the lower extremities (Al'joboori et al., 2021), and may provide a more reliable means of augmenting the effects of motor training in PwMISCI (Estes et al., 2021).

Future studies examining the effectiveness of combined lower extremity motor training and TSS in PwMISCI would be of value.

APPENDIX A. A PILOT STUDY OF INTENSIVE LOCOMOTOR-RELATED SKILL TRAINING AND TRANSCRANIAL DIRECT CURRENT STIMULATION IN CHRONIC SPINAL CORD INJURY.

A.1 Comprehensive list and comparison of participant demographics and baseline characteristics. Continuous variables presented as mean ± standard deviation with *p* values derived from independent-samples t-tests. Categorical variables presented as counts with *p* values derived from chi-square tests.

Characteristics	**MST+tDCS$_{sham}$ (n=14)**	**MST+tDCS (n=11)**	***P***
Age (years)	46.71 ± 14.98	50.45 ± 10.74	0.492
Sex	M=10 / F=4	M=8 / F=3	0.943
Time Since Injury (months)	93.21 ± 85.31	78.45 ± 93.00	0.684
Neurological Level of Injury	C3-C8=13 / T1-T10=1	C3-C8=09 / T1-T10=2	0.495
AIS Classification	C=1 / D=13	C=1 / D=10	0.859
ISNCSCI LEMS (Total Score)	37.14 ± 9.21	41.09 ± 8.34	0.279
SCATS (Combined Score)	4.29 ± 3.34	4.91 ± 4.18	0.682
10MWT Speed (m/sec)	0.72 ± 0.53	0.64 ± 0.51	0.703
2MWT Distance (m)	83.14 ± 49.41	77.12 ± 55.31	0.769
BMI (m/kg^2)	23.30 ± 4.62	26.01 ± 6.09	0.216
Berg Balance Scale (Total Score)	37.07 ± 14.20	41.55 ± 14.38	0.445
Falls Efficacy Scale-I (Total Score)	34.14 ± 9.42	36.73 ± 11.49	0.542
Modified 5-Times Sit-to-Stand (sec)	13.71 ± 5.19	21.88 ± 17.26	0.157†
GXT VO_{2peak} (ml/kg/min)	17.51 ± 5.77	16.23 ± 5.04	0.566
GXT HR_{peak} (beats/min)	134.2 ± 22.7	126.8 ± 20.5	0.407
Smoking Status	***No=14 / Yes=0***	***No=8 / Yes=3***	***0.037***

A.2 Linear mixed-effects model output for walking speed.

N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	-311.013	1	23	57.884	0.000
TIME	Intercept				7	161	11.694	0.000
GROUP	Intercept				1	23	0.095	0.761
TIME x GROUP	Intercept				7	161	0.620	0.739

A.3 Linear mixed-effects model output for walking distance.

N Subjects = 25 N Total Observations = 50								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	425.178	1	0	2.167	1.000
TIME	Intercept				1	23	27.518	0.000
GROUP	Intercept				1	23	0.100	0.755
TIME x GROUP	Intercept				1	23	0.058	0.812

A.4 Linear mixed-effects model output for cadence (stride frequency).

N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	1249.001	1	23	127.946	0.000
TIME	Intercept				7	161	12.705	0.000
GROUP	Intercept				1	23	0.002	0.963
TIME x GROUP	Intercept				7	161	1.391	0.212

A.5 Linear mixed-effects model output for stride length (weaker limb).

N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	1329.920	1	23.000	282.717	0.000
TIME	Intercept				7	160.001	9.727	0.000
GROUP	Intercept				1	23.000	0.565	0.460
TIME x GROUP	Intercept				7	160.001	0.462	0.861

A.6 Linear mixed-effects model output for stride length (stronger limb).

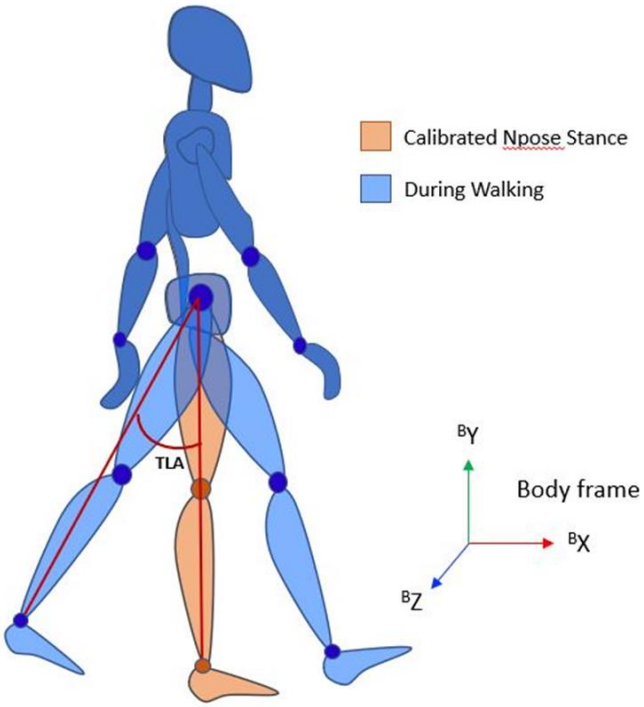
N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	1269.549	1	0.000	43.566	0.000
TIME	Intercept				7	160.001	10.307	0.000
GROUP	Intercept				1	23.000	0.581	0.454
TIME x GROUP	Intercept				7	160.001	0.629	0.731

A.7 Linear mixed-effects model output for step symmetry index (SI).

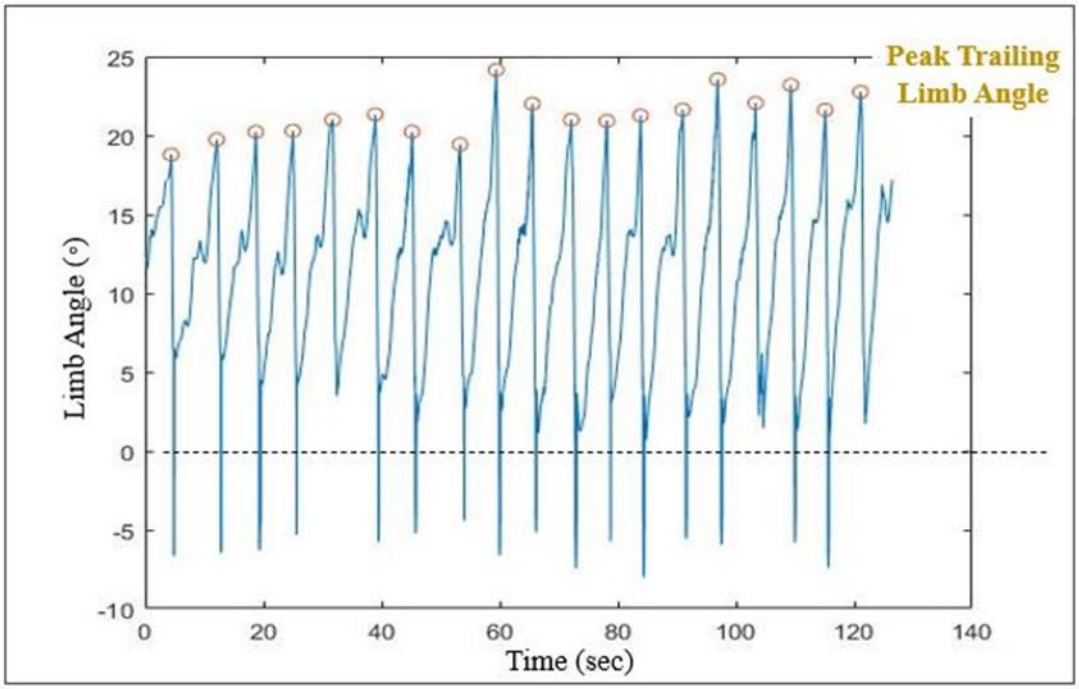
N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	1329.920	1	22.998	22.901	0.000
TIME	Intercept				7	160.004	0.305	0.951
GROUP	Intercept				1	22.998	0.420	0.524
TIME x GROUP	Intercept				7	160.004	0.403	0.899

APPENDIX B. WALKING AND BALANCE OUTCOMES ARE IMPROVED FOLLOWING BRIEF INTENSIVE LOCOMOTOR SKILL TRAINING BUT ARE NOT AUGMENTED BY TDCS IN PERSONS WITH CHRONIC SPINAL CORD INJURY.

B.1 Image depicting calculation of the peak trailing limb angle (TLA) measured as the difference between the ankle position during walking and the ankle position during initial calibration (standing Npose) relative to the hip joint. Positions of anatomical landmarks in the global frame were determined using a link segment (kinematic chain) model. Customized MATLAB code was written to extract sagittal plane kinematics from the Xsens MVN ANALYZE program.



B.2 Representative peak trailing limb angle (TLA) data extracted from a 3D motion capture system using inertial measurement units during a single 10-meter walk trial. Circles represent the peak values used in the analysis to calculate the average peak TLA for each walk trial.



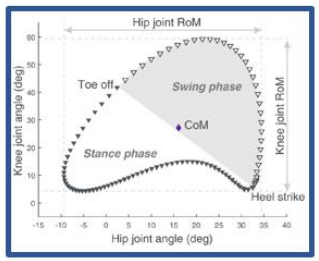
B.3 Linear mixed-effects model output for trailing limb angle (TLA) (stronger limb).

N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	805.507	1	23	681.354	0.000
TIME	Intercept				7	161	3.102	0.004
GROUP	Intercept				1	23	1.248	0.276
TIME x GROUP	Intercept				7	161	0.688	0.682

B.4 Linear mixed-effects model output for trailing limb angle (TLA) (weaker limb).

N Subjects = 25 N Total Observations = 200								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	820.161	1	0	77.484	0.000
TIME	Intercept				7	161	1.720	0.108
GROUP	Intercept				1	23	0.034	0.855
TIME x GROUP	Intercept				7	161	0.711	0.663

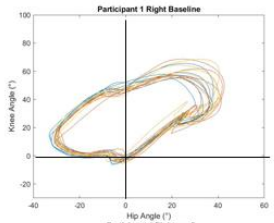
B.5 Hip-knee relative motion plots of the stronger limb among individual participants with spinal cord injury at baseline, Day-1 (D1) and 24-hours post-intervention, Day-5 (D5). Left inset image represents the typical hip-knee angle relationship during a single stride event among non-injured adults (From: (Park et al., 2021)).

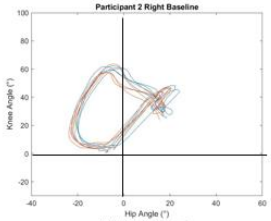


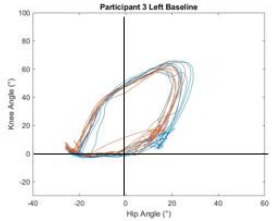
From: Park, et al. *Scientific Reports* 2021

D1

D5







Xsens Error
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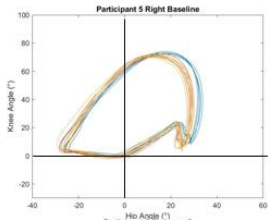
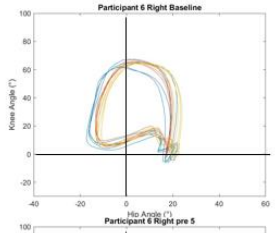
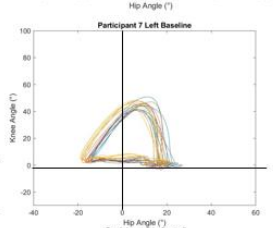
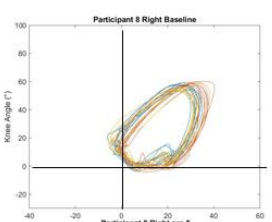


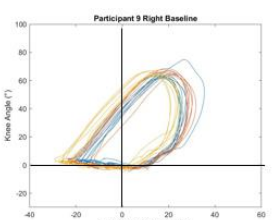
D1

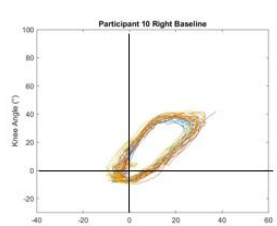
D5











Xsens Error
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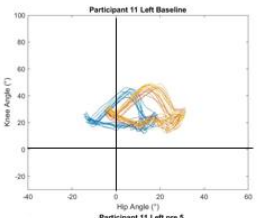
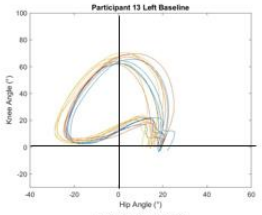
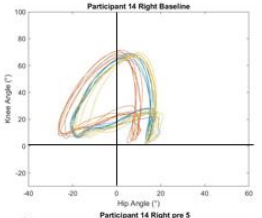
D1


Participant 11 Left Baseline
Knee Angle (°)
Hip Angle (°)


Participant 13 Left Baseline
Knee Angle (°)
Hip Angle (°)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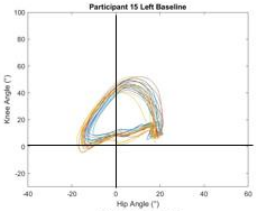
Knee Angle (°)
Hip Angle (°)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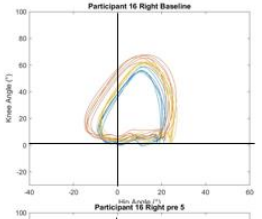
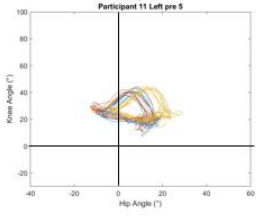
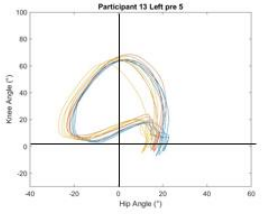
Knee Angle (°)
Hip Angle (°)


Participant 16 Right Baseline
Knee Angle (°)

D5


Participant 11 Left pre 5
Knee Angle (°)
Hip Angle (°)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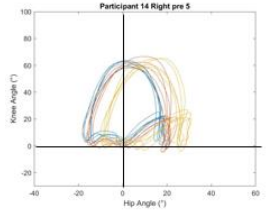
Knee Angle (°)
Hip Angle (°)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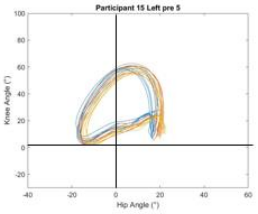
Knee Angle (°)
Hip Angle (°)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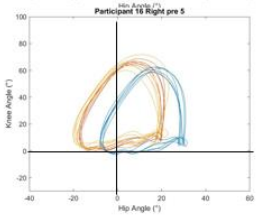
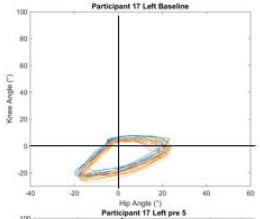
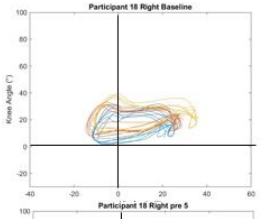
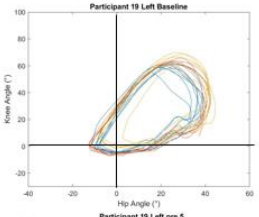
Knee Angle (°)
Hip Angle (°)


Participant 16 Right pre 5
Knee Angle (°)
Hip Angle (°)

D1


Participant 17 Left Baseline
Knee Angle (°)
Hip Angle (°)


Participant 18 Right Baseline
Knee Angle (°)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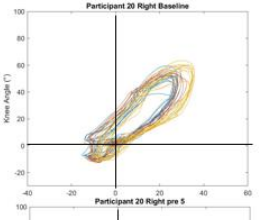
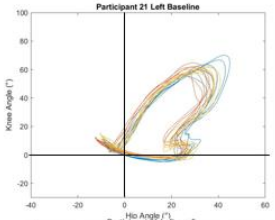
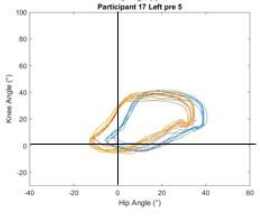
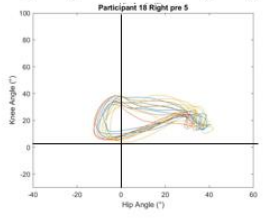
Knee Angle (°)
Hip Angle (°)


Participant 20 Right Baseline
Knee Angle (°)


Participant 21 Left Baseline
Knee Angle (°)
Hip Angle (°)

D5


Participant 17 Left pre 5
Knee Angle (°)
Hip Angle (°)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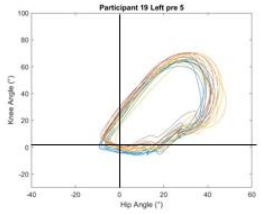
Knee Angle (°)
Hip Angle (°)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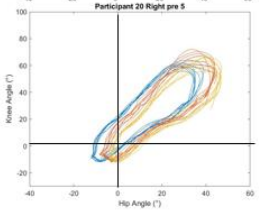
Knee Angle (°)
Hip Angle (°)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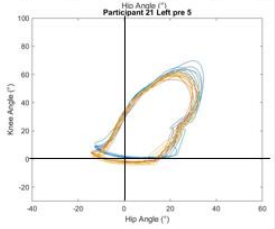
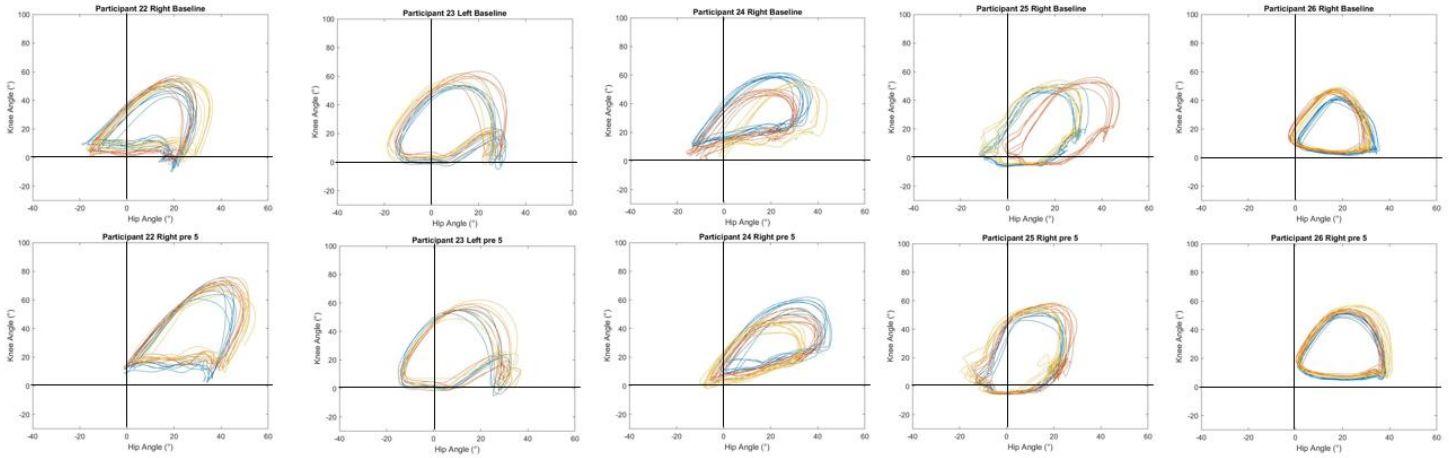
Knee Angle (°)
Hip Angle (°)


Participant 21 Left pre 5
Knee Angle (°)
Hip Angle (°)

D1



D5

B.6 Linear mixed-effects model output for Berg Balance Scale (BBS).

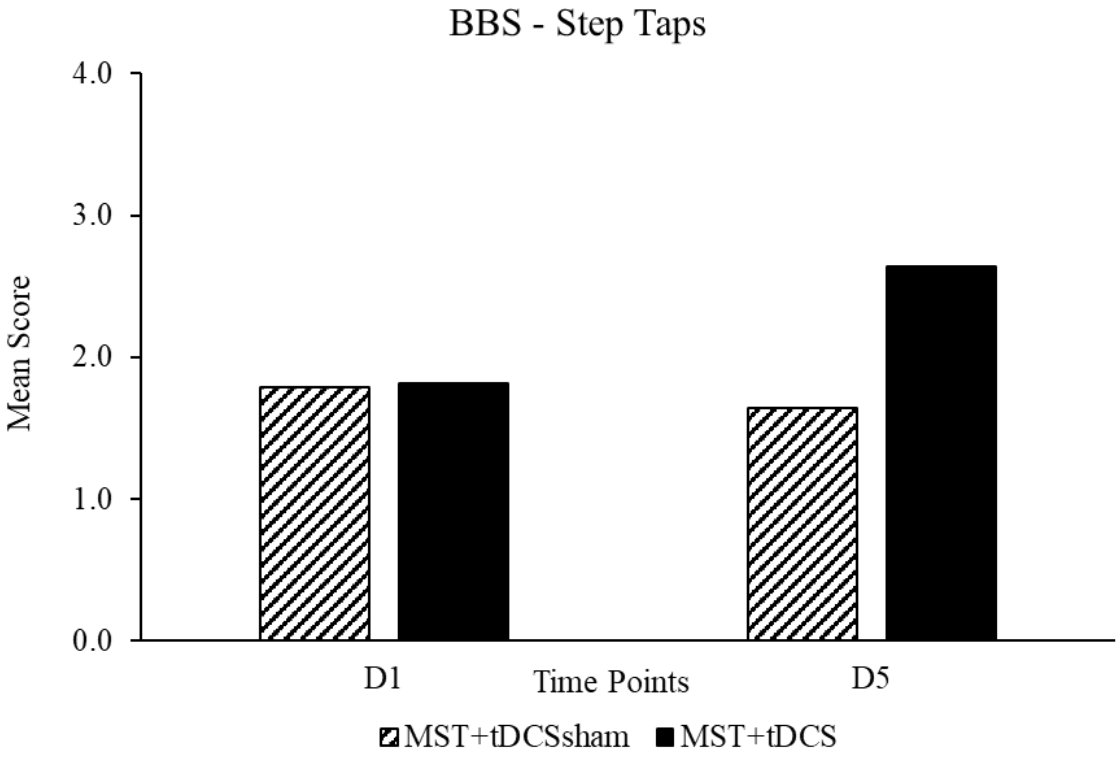
N Subjects = 25 N Total Observations = 50								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	321.880	1	23	211.857	0.000
TIME	Intercept				1	23	7.155	0.014
GROUP	Intercept				1	23	0.596	0.448
TIME x GROUP	Intercept				1	23	0.069	0.795

B.7 Linear mixed-effects model output for Falls Efficacy-International (FES-I).

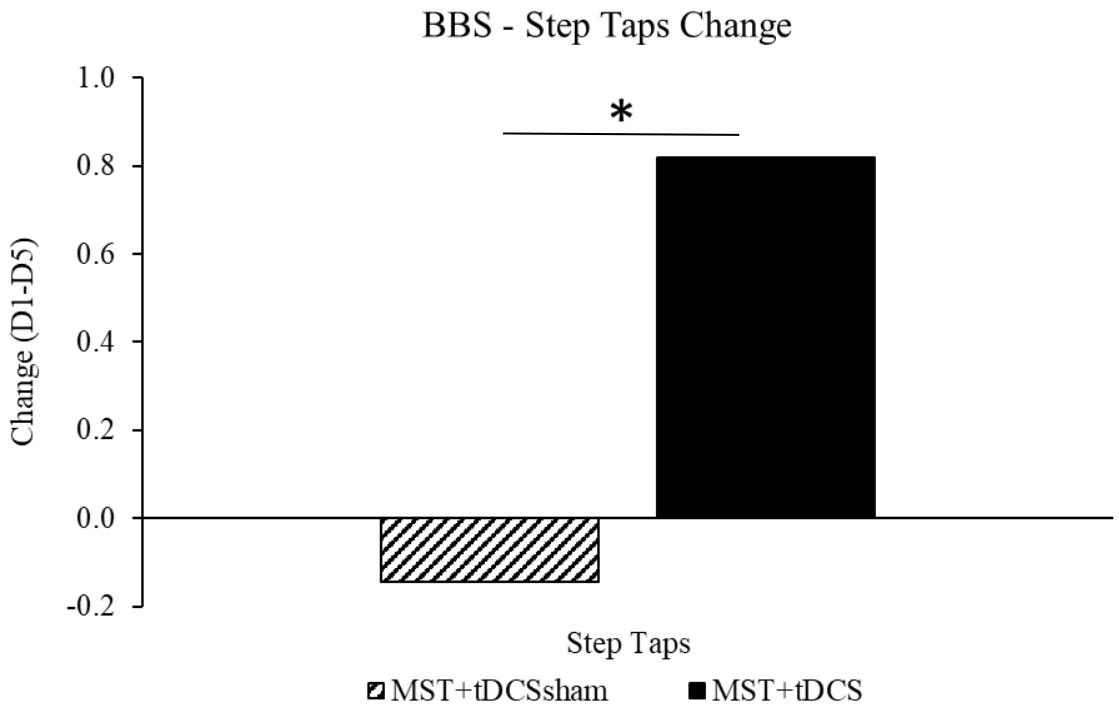
N Subjects = 25 N Total Observations = 50								
Fixed Effects	**Random Effects**	**Parameter Estimation**	**Covariance Structure**	**Model Fit**	**Type III Tests of Fixed Effects**			
	Subjects			**-2 RLL**	**df (numerator)**	**df (denominator)**	**F**	***Sig.***
INTERCEPT		Restricted Maximum Likelihood Estimation	Variance Components	305.677	1	0	315.836	0.000
TIME	Intercept				1	23	12.426	0.002
GROUP	Intercept				1	23	0.300	0.589
TIME x GROUP	Intercept				1	23	0.399	0.534

APPENDIX C. SUPPLEMENTARY FIGURES DEPICTING DATA NOT INCLUDED IN PRIMARY AND SECONDARY ANALYSES

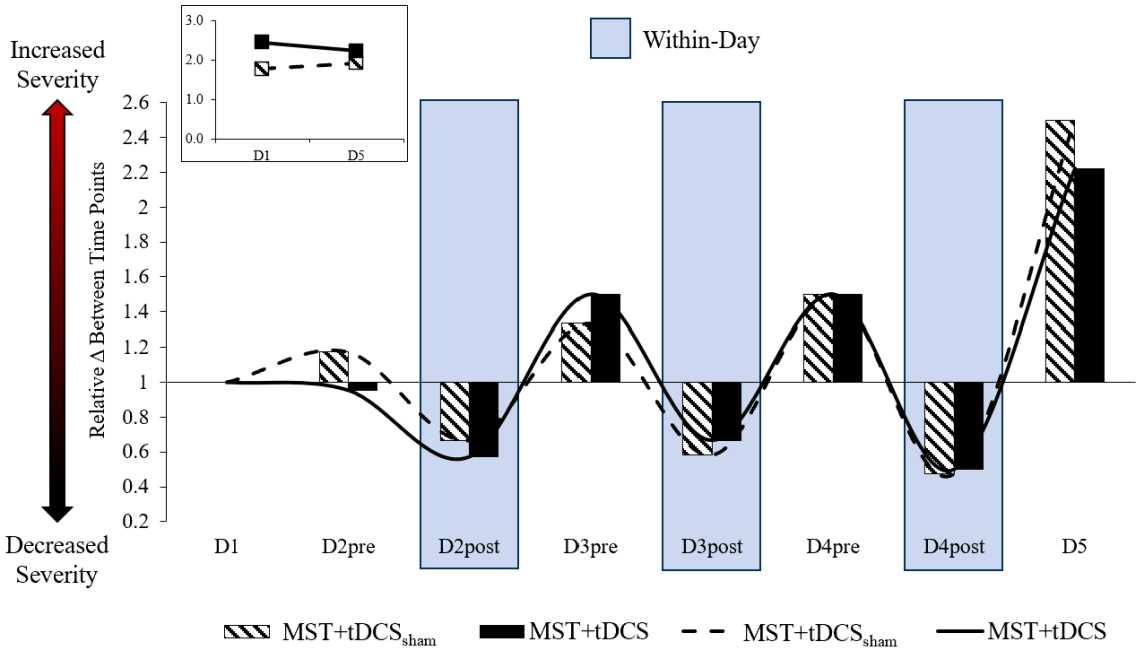
C.1 Supplementary figure depicting mean scores for test item#14 (step tap task) of the Berg Balance Scale (BBS) at baseline, day-1 (D1) and 24-hours post-intervention, day-5 (D5). Hashed bars represent data from the motor skill training plus sham-tDCS group ($MST+tDCS_{sham}$). Solid bars represent data from the motor skill training plus active-tDCS group (MST+tDCS). Higher scores represent better balance performance.



C.2 Supplementary figure depicting significant between-groups difference in the change score for test item#14 (step tap task) of the Berg Balance Scale (BBS) from baseline, day-1 (D1) to 24-hours post-intervention, day-5 (D5). Hashed bar represents the motor skill training plus sham-tDCS group (MST+tDCS$_{sham}$). Solid bar represents the motor skill training plus active-tDCS group (MST+tDCS). Higher scores represent improved balance performance. *Significance determined from independent-samples t-test, p=0.01.



C.3 Supplementary figure depicting relative within- and between-day change in knee extensor spasticity severity score (assessed by SCATS) across five consecutive days. Hashed bars and lines represent data from the motor skill training plus sham-tDCS group (MST+tDCS$_{sham}$). Solid bars and lines represent data from the motor skill training plus active-tDCS group (MST+tDCS). Values above the horizontal line represent increases in spasticity severity between test time-points. Values below the horizontal line represent decreases in spasticity severity between test time-points. Blue shaded regions indicate within-day change in knee extensor spasticity severity before (pre) and after (post) participation in MST. Inset figure depicts the mean SCATS knee extensor spasticity severity score for the MST+tDCS$_{sham}$ and MST+tDCS groups at baseline, day-1 (D1) and 24-hours post-intervention, day-5 (D5). No between-groups differences in spasticity severity were observed.



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