Effects of Spinal Cord Stimulation on Neuromechanics of Gait for Children with Cerebral Palsy

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Abstract

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Cerebral palsy (CP) is one of the largest causes of motor disability in children. Due to an injury in the central nervous system around the time of birth, children with CP have altered motor control and function that affects their movement. Common interventions to support mobility in children with CP often target secondary complications such as bone deformities, muscle contracture, and spasticity. Interventions are needed that can non-invasively support mobility in children with CP while targeting the underlying nervous system injury. Expertise in engineering, biomechanics, neuroscience, and rehabilitation can help to design and evaluate novel interventions for children with CP. This dissertation investigates how three novel interventions: spinal stimulation, interval treadmill training, and exoskeletons impact movement for children with CP.

Transcutaneous spinal cord stimulation (tSCS) is a novel technique for modulating neural activity. Previous research suggests that tSCS can boost sensory feedback as it enters the spinal cord and may be effective for improving motor output when applied during rehabilitation. The evidence thus far for how tSCS may impact movement for children with CP is minimal but suggests that tSCS may improve whole-body motor function and coordination of muscle activity, even after one session of use. We enrolled four children with CP in a pilot study where they received 24 sessions each of short-burst interval treadmill training (SBLTT) only and SBLTT with tSCS. We found that tSCS+SBLTT reduced spasticity while maintaining walking function and reducing self-reported fatigue more than SBLTT only. However, we are continuing to understand the underlying neural and biomechanical changes that drive these functional improvements, as well as more about how these changes translate to community mobility.

Increased sensory information from tSCS+SBLTT may change how the body controls movement. Understanding the biomechanical changes with tSCS+SBLTT can elucidate the mechanisms driving functional improvements. In the same study of four children with CP, we quantified changes in muscle activity and joint kinematics. We found that participants walked in a more upright posture, with more knee and hip extension, after tSCS+SBLTT. Muscle co-contraction was also reduced, primarily in the thigh. Participants also had a reduction in motor control complexity after SBLTT only, but not after tSCS+SBLTT, despite reductions in spasticity. These results suggest that tSCS+SBLTT may improve coordination of movement and lead to more energy efficient walking patterns in children with CP.

One challenge when implementing novel rehabilitation techniques is tracking individual progress. Understanding why and how someone's walking changes with rehabilitation is important for determining the best method for reaching their movement goals. This can be

challenging to quantify due to the natural variability in movement, nonlinear rehabilitation progression, and additional factors that can mask change. We developed a causal modeling and machine learning paradigm to measure the direct effect of SBLTT on step length in children with CP. Using a virtual dataset, we validated that this paradigm can accurately capture nonlinear changes in step length with simulated training data. We then applied the causal modeling and machine learning paradigm to show that three of four children with CP improved step length with SBLTT, even after controlling for changes like treadmill speed and incline. This framework can be used to track individual therapy progression and determine how an intervention is affecting an individual's movement, remaining accurate even when there is high variability in the data.

Another aspect of translating novel techniques into rehabilitative care is understanding how they affect muscle fatigue during training. Overexertion of muscles that causes fatigue can limit motor learning of new tasks. Children with CP fatigue faster than peers, making fatigue an important consideration when developing rehabilitation programs. We quantified how tSCS and a resistive ankle exoskeleton, designed to increase muscle engagement, affected fatigue in nine children with CP. Each participant did 20-minutes of walking on separate days with no devices, tSCS only, bilateral resistive ankle exoskeletons (Exo), and tSCS+Exo. We found that the Exo session had the greatest rate of fatigue within the first 5-minutes of training, while there was an increase in muscle engagement with minimal signs of fatigue during the tSCS+Exo training. These findings suggest that the resistive exoskeleton may be more fatiguing on muscles, but that tSCS reduces the rate of fatigue. The use of these tools together may be beneficial for optimizing engagement in rehabilitation programs while supporting neuroplasticity.

This dissertation contributes to the fields of mechanical engineering, rehabilitation engineering, and neuroscience through a detailed investigation into how novel rehabilitation strategies affect movement for children with CP. We employ methods across these fields to comprehensively deepen our understanding of human movement and evaluating individual responses to rehabilitation. This work will support future translation of novel, non-invasive rehabilitation strategies into clinical care with tools to support how we can optimize and personalize their implementation.

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Chapter 1

INTRODUCTION

Mobility is an important part of everyday life. Mobility includes how we move and interact with our environment and can look different for everyone. Most people walk as their primary mode of mobility with many children beginning to walk around one year of age, but this trajectory looks different for everyone, especially children with disabilities. Children with cerebral palsy (CP), where there is an injury to the central nervous system (CNS) around the time of birth, usually have delayed onset of walking or do not walk at all [1]. For children with CP who are ambulatory, the delay in mobility and often reduced walking function compared to peers affects cognitive, social, and behavioral development. Being unable to keep up playing with peers can limit social interaction and lead to a compounding effect on development, both mentally and physically, as children grow.

While there is no cure for CP, there are many interventions for ambulatory children with CP that focus on maintaining or improving walking function. These include anything from surgical interventions to hippotherapy to treadmill training [2]. Most often, these interventions target secondary health complications that result from CP, not the initial injury to the CNS. Children with CP often have multiple surgeries, from orthopedic to neural surgeries, and may regularly see a physical and/or occupational therapist throughout their life. Therapy is often focused on learning movement based around someone's current abilities and gaining independence in daily activities [3], [4]. Despite these efforts, people with CP report an earlier decline in walking function, greater physical fatigue, and more pain compared to the general population [5], [6]. More effective interventions are needed that are not as burdensome as invasive procedures and provide lasting

change to the body's function, preferably by targeting the initial changes to the CNS rather than secondary effects.

Neuromodulation combined with physical therapy may be a tool to amplify the effectiveness of rehabilitation interventions through greater engagement of the nervous system during training. Neuromodulation is the concept of using electrical or chemical agents to modulate activity in the CNS, our body's control system. Electrical neuromodulation of the spinal cord, known as spinal cord stimulation, has been shown to be an effective tool to accessing neural pathways that are otherwise present but not usable for someone with a neurological injury, such as spinal cord injury [7]–[12]. Non-invasive spinal cord stimulation has recently been used in people with cerebral palsy and has been shown to improve mobility when used in conjunction with physical therapy [13]–[15].

Transcutaneous spinal cord stimulation (tSCS), the focus of this dissertation, is spinal stimulation applied to the skin surface that is hypothesized to amplify sensory feedback entering the spinal cord [16], [17]. The amplified sensory feedback is conceptually similar to increasing error recognition in a control system, and provides more information for the control system, the CNS in the human, to refine the motor control output of the system. This dissertation is focused on the application of tSCS to influence walking function in children with CP. We focus specifically on the neuromechanics of gait, or the combination of the study of the mechanics and control of human movement, including joint kinematics, muscle activity, and spatiotemporal changes in walking. Given how variable rehabilitation and neuromechanics of gait can be, we also apply machine learning in novel ways to better quantify individual, variable, and nonlinear changes in gait with rehabilitation.

1.1 FOCUS OF THE DISSERTATION

This dissertation focuses on understanding how novel interventions targeted at improving walking function in children with CP affect neuromechanics of gait. We use tools from mechanical engineering, neuroscience, and rehabilitation medicine to develop our understanding across disciplines for a more comprehensive assessment of walking and the individual person. Overall, this dissertation focuses on two key themes: how machine learning can be used to quantify individual rehabilitation responses and quantifying the underlying neuromechanical responses to use of tSCS in children with CP.

We start with a four-subject, single-arm pilot study to explore the preliminary effect of tSCS and treadmill training on spasticity, neuromuscular coordination, and walking function in children with CP (Chapter 3). We found that reductions in spasticity were greater after tSCS and treadmill training compared to the same treadmill training without tSCS, and these reductions were sustained after training was complete. Walking function was maintained throughout both interventions. We quantified greater reductions in muscle co-contraction and increases in total joint dynamic range of motion after tSCS compared to training without tSCS. With this same pilot data, we also quantified individual changes in neuromechanics of gait during overground walking for each participant (Chapter 4). We found that participants reached the greatest hip and knee extension after training with tSCS compared to training without tSCS, suggesting a more upright, less fatiguing posture.

We also wanted to further understand how step length, a common rehabilitation outcome for children with CP, changed within and between treadmill training sessions and what the drivers of those changes were. Information about spatiotemporal parameters of gait can help inform the prescribed treatment plan, but it can be challenging to isolate the direct effect of the rehabilitation

program on gait outcomes when many factors change during a training session, such as walking speed. We applied causal modeling and machine learning to isolate these direct effects and validate the model using *in silico* data (Chapter 5). We found these algorithms can accurately identify treatment effects using *in silico* data, such as modeling nonlinearities and maintaining accuracy when there is high variability in the walking patterns. In deploying on our data, we demonstrated that interval treadmill training increased step length in three of four children with CP, even after controlling for treadmill speed, incline, time within session, and side of the body.

Improving our understanding of how to integrate novel devices, such as tSCS, into clinical care will enhance their lasting impact. One challenge can be determining the optimal dosing of physical therapy to challenge a child with CP without overexertion. To better understand optimal dosing, we quantified muscle activity during training with tSCS and a resistive exoskeleton to understand how tSCS may affect muscle fatigue (Chapter 6). We found that muscles fatigued at a faster rate during walking with the resistive exoskeleton, but that combining tSCS with the resistive exoskeleton reduced the rate of fatigue to be more similar to walking without any devices.

1.2 SIGNIFICANCE

The research conducted in this dissertation contributes to the biomechanics, neuroscience, exoskeleton, mechanical engineering, and rehabilitation fields. Understanding the changes in neuromechanics of gait in response to tSCS is important for developing our understanding of how tSCS affects control of movement for children with CP, how to optimize integration of tSCS into clinical care, and how to track training progression for clinical decision-making. By combining traditional clinical assessments with neuromechanical analysis, we can capture the complex and multifactorial response to neuromodulation for children with CP. Thus, the primary contributions of this dissertation include:

Understanding non-invasive interventions that can target changes in the nervous system after neurological injury: Current treatments for children with CP are often invasive and time-consuming, placing large burdens on both the child and parent. Current clinical interventions for children with CP largely fail to directly target the underlying neuropathology, resulting in children undergoing multiple interventions to target the many secondary effects of the initial brain injury [18]. Such interventions include blocking sensory pathways to prevent spasticity or orthopedic surgery to lengthen muscles that result in a need for extensive rehabilitation afterwords. This includes pharmacological approaches which often result in side effects such as decreased walking speed, muscle weakness, and sedation [19]. Neuromodulation is the process of inhibition or excitation in specific areas of the nervous system, either electrically or chemically, to therapeutically modulate neural activity. Neuromodulation is unique to other approaches by focusing on promoting organization through assisting natural use and organization. Neuromodulation, such as spinal cord stimulation, can be used to directly target the CNS after neurological injury [20]. For children with CP, spinal stimulation has the potential to promote organization of the nervous system and result in more coordinated motor output [21]. The focus of spinal cord stimulation is to improve existing neural pathways and optimize their use. This objective is counter to most clinical available treatments that block sensory information or perform orthopedic surgery on musculotendon tissue to work around existing anatomy and reallocate forces. Thus, spinal cord stimulation may be a non-invasive tool to pair with physical therapy for children with CP to support improvements in both voluntary and involuntary function in children with CP with limited negative or permanent side effects. This dissertation evaluates the effects of tSCS combined with treadmill training on children with CP to understand its potential uses for children with CP, a key step in translation to clinical care.

Quantifying the relationship between changes in body structure and function: The ability of neuromodulation to amplify sensory feedback to inform our body's control system may influence both the involuntary (i.e. spasticity), and voluntary (i.e. walking), aspects of sensory integration. The spinal stimulation targets neural pathways in the spinal cord, but this can result in a cascading effect on the nervous system throughout the body, which may cause changes in movement, function, and day-to-day activity, which can in turn influence body structure, i.e. anatomy, and function [22]. Understanding the detailed neuromechanical mechanisms can be used to optimize the delivery of spinal stimulation on an individual basis, while understanding the impact on function and daily life ensures translation of research that is meaningful to the end users: the person with CP and their family. A more comprehensive approach can not only inform our hypotheses for why and how neuromodulation affects movement for children with CP, but it can also help to understand the complex relationships between body structure and function and inform our understanding of the highly heterogeneous population of children with CP. This dissertation quantifies changes in body structure, function, and activities of daily living to understand responses to rehabilitation across the spectrum.

Developing techniques to quantify individual responses to rehabilitation: Given the complexities of rehabilitation for children with CP, such as physical therapy, individualized rehabilitation can help to optimize outcomes. A rehabilitation intervention may be deemed ineffective if not implemented correctly. Given the heterogeneity of the population of people with CP, it is likely that one intervention and method of delivery is not going to have the same outcomes for each person. In some cases, certain participants are deemed 'non-responders' with a lack of understanding of why some respond while others do not or how to transcend this gap. This dissertation develops and validates a method using causal modeling and machine learning to

understand the interactions of participant differences, design of rehabilitation programs, and the training itself on movement outcomes. This framework provides more detailed information on drivers of response to rehabilitation and can be used as a tool for informing clinicians on how to adapt a rehabilitation program, such as physical therapy, to target a person's desired outcome.

1.3 Dissertation Overview

This dissertation includes two experimental studies, (1) a multi-year clinical trial combining tSCS with physical therapy and (2) an acute study focused on quantifying single-session changes with tSCS use and a robotic exoskeleton. Chapter 2 provides an overview of relevant background information to provide additional context to the subsequent chapters. Chapter 3 quantifies the effects of tSCS and treadmill training on spasticity, walking function, and neuromechanics of gait on four children with CP [23]. Chapter 4 expands on the neuromechanics of gait for each of the four children with CP, focusing on their individual changes and how this can inform the mechanisms behind how tSCS functions for children with CP [24]. Chapter 5 applies machine learning and causal modeling to isolate the direct effects of training on spatiotemporal parameters of walking withing and across sessions to better inform clinical decision-making [25]. Chapter 6 focuses on how tSCS affects muscle fatigue during training to better understand how it may be implemented into clinical care (Caskey et al. *In preparation*). The final chapter of this dissertation summarizes the key findings, applications of this work, and areas of future research. Throughout the dissertation, the pronoun 'we' is used to recognize the collaborative nature of the research across the multidisciplinary team. The individuals who contributed to these studies are provided at the beginning of each chapter.

Chapter 2

BACKGROUND

2.1 CEREBRAL PALSY

Cerebral Palsy (CP) affects 0.32% of children [26], making it one of the leading neurological disabilities among children [27]. CP is defined as an injury to the brain around the time of birth [27]. Since the brain injury occurs at such a young age, CP affects the development of not only the brain, but also the spinal cord and musculoskeletal systems that rely on supraspinal input and motor experience to guide development [28]. Altered development disrupts early neuroplasticity – the process of constant development and changing of pathways in our CNS. As a result, children with CP often have secondary complications, such as reduced selective motor control [29], [30], musculoskeletal contractures and weakness from modified muscle composition [31], and spasticity [27]. Spasticity is characterized as a hyperactive stretch reflex that can make it challenging to relax and lengthen muscles and affects approximately 85% of children with CP [32]. Collectively, these changes in neurophysiology and anatomy affect neuromuscular control of movement, or how the brain and spinal cord control muscle activity to generate movement, in children with CP.

2.1.1 Neurophysiology

A brain injury early in life affects the developing spinal cord and corticospinal tracts. Children with CP do not have the same activity-dependent withdrawal of corticospinal pathways as their peers [33], a pruning process that helps refine motor control and sensory integration [34]. While development of this corticospinal tract comes later in development, the development of afferent pathways into the spinal cord occurs much earlier [35]. Sensory information into the spinal cord via afferent pathways can independently activate spinal circuits, such as central pattern generators, and reflex pathways. Without the expected corticospinal input, which primarily

includes inhibition, these spinal pathways remain hyperactive and disorganized [36], [37]. Rewiring of the brain and spinal cord with development is determined by several factors including supraspinal input from the brain, sensory input from the peripheral nervous system, and daily use through motor function [38], [39]. This altered neuroplasticity affects the sensorimotor system in children with CP, likely a cause of spasticity, reduced motor control, and reduced intersegmental coordination during movement [29], [40].

2.1.2 Ambulatory Children

The Gross Motor Function Classification System (GMFCS) is commonly used to classify motor function in people with cerebral palsy [27]. GFMCS levels range from I-V, and the definitions change based on a child's age. For children 6-12 years old, GFMCS Level I is someone who can walk and run, but has limitations in speed, balance, and coordination. Up to GMFCS level III is generally considered ambulatory, and individuals in GMFCS level III often use a hand-held mobility device to walk and wheeled mobility for longer distances. Approximately 70% of children with CP are ambulatory in GMFCS levels I-III, meaning walking is their primary mode of mobility [32], [41]. However, children with CP are less active than their typically developing peers [42]–[44]. This is likely due to an increase in energy consumption during walking that contributes to slower walking speeds and greater fatigue, making it challenging for children with CP to keep up with peers during daily activities like play or sports. As ambulatory children with CP age into adulthood, approximately 39% report a decline in walking function by 45 years of age [6]. This is a common frustration among young adults with CP, making maintenance of walking function a primary rehabilitation goal for individuals with CP.

2.1.3 Neuromechanics of Gait

The most common subtype of CP is spastic CP, affecting approximately 80% of children with CP [32]. The most common gait patterns among individuals with spastic CP include equinus gait, also known as toe walking, crouch gait, also known as flexed knee walking, or some combination of the two [45]. In equinus gait, the ankle remains plantar flexed passed 90 degrees throughout most of the gait cycle with minimal movement [46]. Spasticity in the plantarflexors and/or poor motor control of these muscles are likely causes of equinus gait. In crouch gait, the hip and knee remain excessively flexed, most often either from spasticity in the hamstrings or gastrocnemius or poor motor control of these muscles [46], [47]. To help with the lengthening of muscles and prevent the development of contractures, children with CP are often prescribed ankle-foot orthotics (AFOs) that help position the ankle in a more dorsiflexed position. It is recommended that children wear these at least six hours a day to stretch their muscles [48]. Compared to non-AFO users, AFO users also have longer step lengths, faster walking speeds, and gait mechanics more similar to typically developing peers [49]. Many children will also often use a cane or walker during ambulation as additional support for movement.

Children with CP also often have reduced motor control, or the inability to selectively activate muscles to generate movement, resulting in less coordinated muscle activity [38], [50]. As a result, some muscle activations can counteract each other and lead to altered gait neuromechanics including increased co-contraction in antagonistic muscle pairs [51]. This can alter gait patterns and contribute to increased energy consumption during movement. Children with CP walk with energy consumption 2-3 times greater than their peers [52]–[54], likely because of increased demand on muscles and reduced muscle endurance for individuals with CP [55].

2.1.4 Surgical and Pharmacological Treatment

Treatment of spasticity is one of the main targets for children with CP. Common and effective interventions targeting reducing spasticity include: Botulinum Toxin Type-A injections (BoNT-A), baclofen, and selective dorsal rhizotomy (SDR). BoNT-A is one of the most common treatments and involves an injection into the muscle to inhibit the release of neurotransmitters required to generate force in the muscle [56]. This results in reductions in spasticity lasting 3-6 months, but the muscle weakness lasts even longer [56], [57]. BoNT-A produces short-term reductions in spasticity and may also improve gross motor function, but the results are temporary and repeated treatments decrease effectiveness and increase detrimental effects on muscle strength [58], [59]. Baclofen is a medication that can be taken orally or with an intrathecal pump. Baclofen primarily works in the spinal cord to block excitatory neurotransmitters and prevent spinal reflexes [60]. However, the effectiveness of baclofen for reducing spasticity is mixed, especially for ambulatory children with CP [61]. SDR is a permanent surgery where afferent pathways in the spinal cord are severed, completely altering the input of sensory information into the body. SDR leads to large reductions in spasticity, but it requires extensive rehabilitation to relearn walking and other tasks of daily living. There are no known benefits of SDR in the long-term for reducing orthopedic surgery, requiring further spasticity treatment, improving walking function, or increasing quality of life [18], [62]. These common treatments for spasticity in children with CP target changes in sensory, or afferent, pathways, such as surgically cutting spinal pathways with SDR or pharmacologically inhibiting neural pathways with medicines like baclofen [19]. These treatments block afferent pathways to reduce sensory feedback and limit hyperactivity that contribute to spasticity and poor motor control [27], [63]. While these approaches reduce spasticity, the long-term impacts on walking function are debated [56], [64]–[66] and may actually

have detrimental effects on function and development [67], [68]. Increasing, rather than eliminating or reducing sensory feedback, may be more valuable to support neuroplasticity and function in CP and affect both voluntary and involuntary motor control [34].

In some cases, orthopedic surgery may be considered to maintain alignment and prevent the development of contractures to help maintain mobility [2]. These procedures are referred to as multi-level surgery (MLS) and typically involve multiple procedures such as muscle-tendon lengthening, osteotomies, and tendon transfers [69]. Prior research has suggested that MLS leads to inconsistent improvements in gross motor function, walking speed, and gait pattern [70]. Clinical gait analysis has been a valuable tool in planning and evaluating the effectiveness of MLS, with improvements typically seen in the knee dynamic range, ankle dorsiflexion, and hip rotation [69]. Orthopedic surgery, however, is not expected to affect spasticity or motor control. Thus, there may remain uncoordinated muscle activity that prevents changes in movement and growth after surgery.

Children with CP also usually receive physical therapy after these treatments and throughout their childhood. After treatment, additional, intensive therapy is often required to learn how to adapt to the changes to the sensory and motor systems. Generating active, task-specific practices that are also engaging for children is critical to support learning and neuroplasticity [71]. There is substantial evidence for training-based therapy, such as mobility or treadmill training [2]. The objectives of physical therapy may include building strength, developing coordinated movement, increasing flexibility, or focusing on walking and mobility. While physical therapy requires a commitment of time, it is completely non-invasive and is focused around supporting a more active lifestyle to improve and/or prevent decline in function [72].

2.2 Non-Invasive Rehabilitation for Ambulatory Children with Cerebral Palsy

Physical therapy can be designed to offer repetition of movements to create an environment for motor learning. Sensory feedback provided during learning has been shown to be critical for generating movement [73], [74] and for functional recovery in both humans and animals with neurologic injuries [39], [75]. Increased sensory feedback about a target movement can support long-term neuroplasticity, helping the brain and spinal cord rewire to optimize performance of targeted tasks [76]–[78]. This includes self-generated, task-specific, repetitive movements that are enjoyable to children and increase engagement [2], [79], [80]. These principles are often brought into the design of physical therapy focused on improving walking function for ambulatory children with CP. While there is no standard of care for children with CP, common therapeutic approaches targeting walking function include strength, mobility, or treadmill training. Interventions that focus on tasks used in daily life, use self-generated movements, offered at high intensity, and with a goal set by the parent or child are most effective [2]. In this dissertation, we investigated the individual and combined effects of interventions designed to address sensory feedback and promote neuroplasticity during physical therapy: short-burst interval locomotor treadmill training, haptic and audiovisual biofeedback, and non-invasive spinal cord stimulation.

2.2.1 Short-burst Interval Locomotor Treadmill Training

Gait training, such as treadmill training with and without bodyweight support, has been shown to be most effective for improving gait speed in children with CP [81]. Short-burst interval locomotor treadmill training (SBLTT) is a novel type of treadmill training designed to mimic the highly variable walking patterns of typically developing children [82], [83]. Children's physical activity in daily life typically involves short bursts of movement at varying levels of intensity. While previous treadmill training for children with CP did not include varying intensities of

movement, SBLTT is a 30-minute training where every 30-secounds the treadmill speed transitions from a slow-to-moderate speed to a fast speed. These speeds are initialized based on an individual child's baseline overground walking speed. Within and between successive training sessions, the slow-to-moderate speed remains consistent, while the fast speed changes based on a participant's perceived exertion. Four to ten weeks of SBLTT has been shown to improve walking speed, endurance, functional mobility, and community mobility for up to six weeks after training is complete [80]. SBLTT may have benefits over other forms of treadmill training because it is founded in ideas of repetition, learning, and creating a challenging task. Children also wear their prescribed ankle foot orthoses and footwear combinations, if applicable, during SBLTT to mimic walking in the community and promote stabilization during the stance phase to encourage fast speeds. They also engage in a low mental activity, such as watching a television show or listening to an audiobook, while walking to promote automaticity during stepping, more similar to daily life.

2.2.2 Haptic and Audiovisual Biofeedback

In addition to standard treadmill training, additional tools may be used to target learning the desired movement pattern. Audiovisual feedback, such as interactive games providing information about step length, joint kinematics, or muscle activation, can teach a child how to change their movement [84]–[87]. Timing of this feedback with an opportunity to learn the expected information is important for translating the learning objective into an actionable change. Manual assistance by a physical therapist or exoskeletons designed to provide either assistance or resistance can be used to increase external sensory feedback and guide desired motions and have been shown to be effective for gait training in children with CP [88], [89]. In just six training sessions, a resistive exoskeleton at the ankle has been shown to increase muscle strength [90] and

motor control complexity in children with CP [91]. Walking with active assistance or resistance via an exoskeleton can provide increased sensory experience during walking to help with step generation and may improve walking speed and spasticity in CP [92], [93].

Increased feedback during training, either with audiovisual or haptic cues, currently create variable effects across individuals and may require continued training to maintain improvements, leaving many questions to be answered before clinical implementation [94]. While this research suggests external feedback from these devices and therapy methods may amplify sensory feedback and support function, the changes in neuromuscular control of movement and resulting neuromechanics with these new training methods are not well understood.

2.2.3 Transcutaneous Spinal Cord Stimulation

There is emerging evidence that non-invasive electrical neuromodulation can be used to influence neural excitability, especially when paired with repetitive, task-specific training. Electrical neuromodulation refers to using stimulation to modulate nervous system function [20]. Electrical stimulation of the spinal cord, both invasively with epidural stimulation and non-invasively with transcutaneous spinal cord stimulation (tSCS), has been shown to target activation of 1a afferent proprioceptive pathways [95], [96]. The convex nature, large size, and myelination of these posterior root fibers as they enter the spinal cord create an optimal position for activation with a stimulating electrode placed over the spinal cord [96]–[98].

Electrical stimulation at high intensities above motor threshold delivered over the L1-T11 vertebrae, where sensory information from the lower extremities enters the spinal cord, has been shown to generate a stepping pattern in people with complete spinal cord injury (SCI) [99]. It is hypothesized that this electrical stimulation activates central pattern generators in the spinal cord that can produce rhythmic stepping patterns without any supraspinal input. Central pattern

generators are thought to control groups of muscles that work together to create a step reflex-like pattern [100]. Electrical stimulation to the spine generates these stepping-like patterns with only stimulation to the posterior root fibers in the spine that carry afferent information [101], [102]. These afferent pathways then project onto motor neurons via communication through both polysynaptic and monosynaptic connections to generate movement [103], [104].

Repeated use of spinal cord stimulation at sub-threshold intensities paired with afferent activity in body positioning, however, can lead to lasting changes in the neural circuitry when stimulation is turned off. Sub-motor threshold stimulation does not trigger immediate motor responses, but rather increases the resting potential of the afferent neurons so that less additional neuronal input is required for the sensory information to generate a motor response [105] (Figure 2.1). Applying sub-threshold stimulation during physical therapy with clinician-supervision on proper alignment can increase the amount of sensory information about the activity being transmitted into the spinal cord relative to surrounding noise [106], [107]. The more that the firing of the sensory neurons generates a firing of the motor neurons, the stronger this pathway becomes, a process known as Hebbian plasticity [108]. The reorganization of the nervous system is activity-dependent on the firing of sensory and motor pathways and can be boosted with sub-threshold stimulation [109].

This reorganization of afferent pathways that are disorganized after brain or spinal cord injury can occur with repeated use of spinal stimulation with repetitive, activity-specific, physical therapy [10] through the engagement of both spinal interneurons and supraspinal centers [110], [111]. For individuals with incomplete spinal cord injury (SCI), just 30 minutes of tSCS has been shown to increase joint passive range of motion, modulate spinal excitability, reduce spasticity, improve coordination of volitional multi-joint movement, and increase walking speed [97], [107],

[112]. Combined with task-specific training over several weeks, tSCS targeting afferent feedback can lead to improved walking function and coordination of movement [113] sustained months after the training is completed [78]. While the research on how tSCS affects motor function has been primarily focused on individuals with SCI, the evidence that tSCS can affect both spinal and supraspinal networks suggests it may be effective for people with neurological injury in the brain, such as individuals post-stroke or with cerebral palsy [21], [111]. The ability of tSCS to target both spinal and supraspinal circuitry makes it particularly interesting for use in children with CP given the effect of reduced supraspinal cord input on spinal development [36], [37]. The ability of tSCS to increase activity-dependent mechanisms in the spinal cord through increased afferent feedback may have an impact on both the spinal and supraspinal connections that are affected in someone with CP [21], [111], [113].

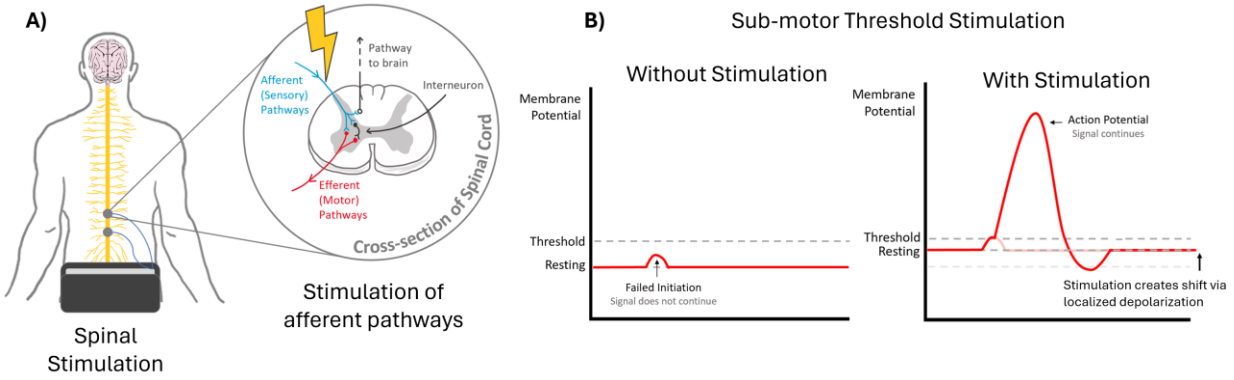

Figure 2.1 A) Diagram of non-invasive spinal stimulation being applied to the thoracic and lumbar regions of the spine. Spinal stimulation is hypothesized to target the afferent (sensory) pathways as they enter the spinal cord. B) Diagram of how sub-motor threshold stimulation is hypothesized to increase the resting threshold to then require less initiation to propagate an action potential.

A handful of researchers have begun using tSCS for children with CP over the past 10 years. Prior work has suggested tSCS applied during 30-minutes of treadmill walking can reduce muscle co-contraction, enable more coordinated joint movement, and lead to an increase in step length for some individuals with CP [17]. Other groups have also reported that tSCS paired with physical

therapy over 15+ sessions with can reduce muscle co-contraction, increase strength output, increase gross motor function, and improve quality of life for children with CP [13]–[15]. Recently, 16 sessions of tSCS with activity-based neurorehabilitation therapy led to reductions in spasticity for children of GMFCS Level V more than a sham stimulation, while there was no change in spasticity for children of lower GMFCS levels [15]. These results suggest that, when paired with repetitive, task specific training, tSCS can lead to sustained activity-dependent neuroplasticity that results in a reorganization of the afferent and efferent pathways that generate movement in children with CP [21]. These findings, however, remain preliminary. We lack a complete understanding of which therapy is best to pair with tSCS, how to optimize dosing and amplitude of stimulation, how lasting these effects are, and why some individuals respond differently. A focus on understanding how tSCS affects the neuromechanics of movement could be helpful in translating our understanding of how the hypothesized neural changes translate to changes in neurophysiology and walking function.

2.3 Optimizing Rehabilitation

As new technologies and interventions continue to be researched and implemented into clinical care, there become more options around determining the best line of action for an individual person. Tracking progress can be challenging during several weeks of rehabilitation because many factors might influence how someone progresses through therapy. For example, with SBLTT, the fast speeds can change based on perceived exertion within and between sessions [80]. It might initially seem positive to see an increase in speed but change in speed may be the only driver of the change in step length. It can be challenging to know if an increase in step length across sessions is due to an increase in speed, adjustment in treadmill incline, or other factors. Understanding what drives a change in the desired outcome can help inform the prescription of

physical therapy to meet individual needs and determine if they are progressing towards target rehabilitation outcomes during actual training sessions. This dissertation will, in part, focus on modeling the relationship between intervention parameters, individual characters, and other factors and their effect on the treatment outcomes.

All the novel techniques assessed throughout this dissertation can be implemented in a variety of ways. With transcutaneous spinal cord stimulation, for example, we deliver it alongside physical therapy, but the choice of physical therapy activity can depend on the individual's movement goals. We also modulate the amplitude of the stimulation, which is thought to vary between individuals and depend on factors such as: age, size, location and extent of their injury, and even the position they are in during the delivery of stimulation [17], [114], [115]. While the research suggests that these are important considerations, we lack empirical evidence of what information should be used when determining the optimal delivery of spinal cord stimulation and other novel technologies.

This dissertation developed a causal model and machine learning framework to track individualized rehabilitation. While these methods have been used either individually or together to understand treatment outcomes across a population [116]–[119], this dissertation will focus on tracking individual changes over time. We will also track changes in neuromechanics before, during, and after use with tSCS, treadmill training, and exoskeletons. This comprehensive evaluation will contribute to our understanding of how these novel inventions affect movement and how quickly this response is to be expected to contribute to tracking function and individual progression. Together, these data collections, analysis, and modeling techniques will allow for better understanding of our interventions and how to provide more personalized care.

Chapter 3

TRANSCUTANEOUS SPINAL STIMULATION AND SHORT-BURST INTERVAL TREADMILL TRAINING IN CHILDREN WITH CEREBRAL PALSY: A PILOT STUDY

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3.1 ABSTRACT

The purpose of this pilot study was to evaluate the effects of transcutaneous spinal cord stimulation (tSCS) and short-burst interval locomotor treadmill training (SBLTT) on spasticity and mobility in children with cerebral palsy (CP). We employed a single-arm design with two interventions: SBLTT only and tSCS + SBLTT in four children with CP. Spasticity, neuromuscular coordination, and walking function in were evaluated before and immediately after, and at 8-weeks following each intervention. Spasticity, measured via the Modified Ashworth Scale, reduced in four lower-extremity muscles after tSCS + SBLTT (1.40 ± 0.22) more than SBLTT only (0.43 ± 0.39). One-minute walk test distance was maintained during both interventions. tSCS + SBLTT led to improvements in peak hip and knee extension (4.9 ± 7.3° and 6.5 ± 7.7°), that drove greater joint dynamic range of 4.3 ± 2.4° and 3.8 ± 8.7° at the hip and knee, respectively. Children and parents reported a reduction in fatigue and improved gait outcomes after tSCS + SBLTT. Improvements in spasticity and walking function were sustained for 8 weeks after tSCS + SBLTT. These preliminary results suggest that tSCS + SBLTT may improve spasticity while simultaneously maintaining neuromuscular coordination and walking function in ambulatory children with CP. This work provides preliminary evidence on the effects of tSCS and the combination of tSCS + SBLTT in children with CP.

3.2 INTRODUCTION

Cerebral palsy (CP) is a disorder of movement and posture caused by non-progressive damage to the developing brain. While CP is primarily a neurological disorder, it also affects the development of neuromuscular and skeletal systems, which negatively impacts mobility and participation in daily activities [27], [43], [50]. Development of corticospinal circuits are impacted

in CP, leading to secondary complications such as altered motor control and muscle spasticity [29], [120].

Eighty-five percent of children with CP present with spasticity [121], which is characterized by a velocity-dependent increase in muscle tone. Spasticity is a major contributor to reduced function and increased discomfort in children with CP, limiting gross motor function during activities such as walking [122]. Current spasticity treatments reduce spasticity but do not consistently translate to improved muscle activity and walking function without extensive additional rehabilitation [65], [123]–[125]. New interventions that can simultaneously reduce spasticity and improve walking function are needed.

Non-invasive neuromodulation may be an alternative approach that can improve outcomes in CP when combined with physical therapy. Transcutaneous spinal cord stimulation (tSCS) is a novel, non-invasive neuromodulation technique that can modulate spinal and supraspinal circuits [12], [21] especially when implemented with physical therapy [78]. Use of tSCS with physical therapy has reduced spasticity and improved motor function in people with spinal cord injury and CP [14], [15], [77], [78]. In children with CP, a single session of tSCS improved coordination of walking and muscle activation [17], while repeated sessions with bodyweight supported treadmill training or activity-based neurorehabilitation therapy improved walking biomechanics and gross motor function, respectively [13]–[15].

While these recent results support using tSCS for children with CP, the impacts on spasticity and walking function in the lab and community have not been investigated. We hypothesized that tSCS may have simultaneous benefits to spasticity and mobility for children with CP. By amplifying afferent feedback, tSCS may guide reorganization of the spinal and supraspinal circuits targeting different mechanisms than current spasticity treatments, including botulinum toxin type-

A injections, baclofen, and selective dorsal rhizotomy [21]. These treatments attempt to reduce muscle activity by inhibiting neural pathways, but often have side effects that result in inconsistent and unsatisfactory changes to walking function without the addition of other interventions, such as physical therapy [18].

The objective of this pilot study was to evaluate the effects of tSCS on spasticity and mobility in children with CP. We evaluated tSCS combined with a unique physical therapy routine specifically designed to improve mobility in children with CP, short-burst interval locomotor treadmill training (SBLTT) compared to SBLTT alone. For children with CP, SBLTT improves walking speed, endurance, and community walking [80]. We hypothesized that tSCS combined with SBLTT would reduce spasticity and improve motor function more than SBLTT alone, and result in improved biomechanics, walking function and community mobility. To test this hypothesis, we compared outcome measures at the completion of each intervention, and after 8-weeks following each intervention.

3.3 METHODS

3.3.1 Study Design

We conducted a single-arm pilot study with two interventions (Figure 3.1). All participants received 24 sessions of SBLTT first, and then 24 sessions of tSCS combined with SBLTT (tSCS + SBLTT). Outcomes were collected at the start of the study, then at the conclusion of each intervention, and at an 8-week follow-up timepoint after each intervention. All visits were conducted at the University of Washington, with one exception. Due to family availability, researchers traveled to the home of one participant (P02) for most training visits, using a family treadmill for SBLTT. The participant visited the lab at least once per week for assessments. This

study was approved by the University of Washington Human Subjects Division (IRB identifier: STUDY00008896) and was registered at ClinicalTrials.gov (NCT04467437).

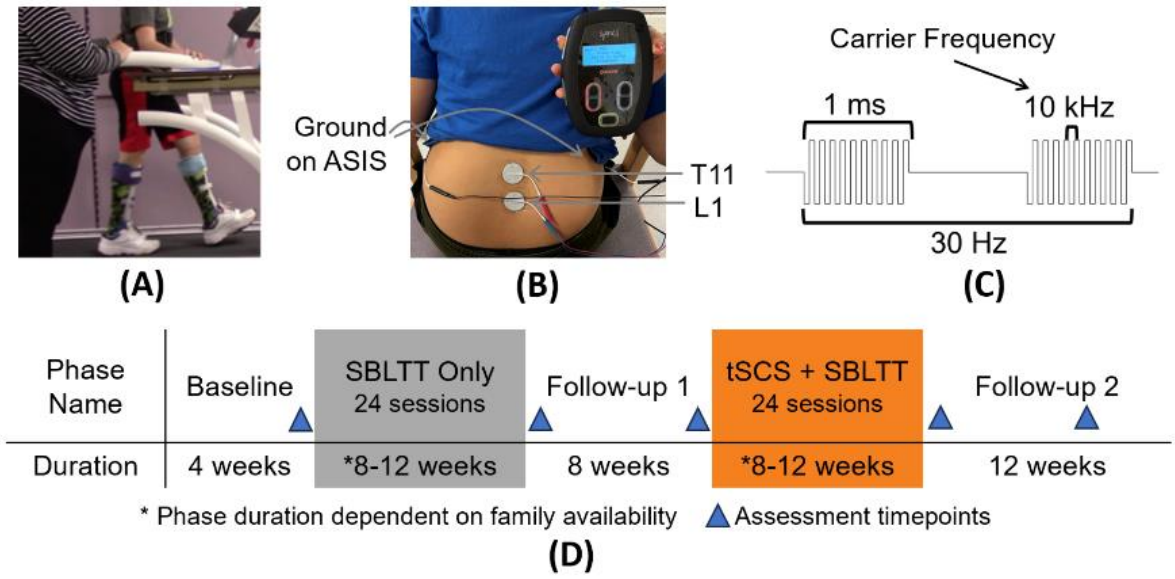

Figure 3.1 A) Short-burst interval locomotor treadmill training (SBLTT) with contact guard assist. B) Investigative spinal cord neuromodulation device (SpineX, Inc.) with stimulating electrodes on the T11 and L1 dorsal spinous processes and two ground electrodes on the anterior superior iliac spine (ASIS - not visible). C) Spinal stimulation waveform with 10 kHz carrier frequency. D) Protocol timeline including the assessments before and after each intervention and after 8 weeks of follow-up. tSCS = transcutaneous spinal cord stimulation.

During both intervention phases, SBLTT was delivered for 30 minutes at each visit following a previously established protocol [13]. SBLTT provides intensive walking practice in which children walk with alternating 30-second bursts of slow and fast speeds, mimicking children's natural walking patterns. During SBLTT, the slow speed was kept constant across all sessions, while the fast speed was increased within and across sessions based on perceived exertion as measured by both clinical observation and the children's OMNI Scale of Perceived Exertion [126]. SBLTT was preceded by a 5-to-15-minute active warm-up and concluded with a 5-minute active cool-down. Warm-up and cool-down activities included overground walking, playing, or walking at a low, steady speed on the treadmill. Rest breaks were provided as needed.

During tSCS + SBLTT, the parameters and application of the investigative spinal cord neuromodulation device (SpineX, Inc.) followed previously reported protocols [17]. Stimulation was applied using adhesive gel electrodes with the cathodes delivering stimulation placed just below the T11 and L1 spinous processes using 3.2 cm round electrodes to target myotomes of the lower extremity muscles and for consistency with prior work [13]. The anodes, serving as the ground electrodes, were 5.1 x 8.6 cm rectangular electrodes placed over the anterior, superior iliac spine (ASIS) (Figure 3.1B). During each visit, stimulation was applied throughout all activities, including warm-up, SBLTT, rest breaks, and cool-down for an average of 56 ± 10 minutes. Amplitude for the sub-motor threshold stimulation was determined based on three factors for each subject: 1) participant reported sensation beneath the cathodes, 2) children's self-report of the ease of walking, and 3) a physical therapist's clinical observation of gait quality and participant's behavior.

3.3.2 Participants

We enrolled ambulatory children with spastic CP Gross Motor Function Classification System (GMFCS) Levels I-II who were not currently taking spasticity management medications, did not have a history of selective dorsal rhizotomy, and had not undergone a lower extremity surgery or botulinum toxin injections in the past 1 year. Four children with CP participated in the study (Table 3.1). Two participants, P02 and P03, weaned off their daily use of baclofen 2-weeks before starting the study. Another participant, P01 took baclofen as needed prior to the study and took 5 mg once during the SBLTT phase. Participants had not received any botulinum toxin injections or orthopedic surgery before joining the study, except P01 who had botulinum toxin injections 9 years prior. Children and parents were informed of the study procedures and signed an informed consent and age-appropriate assent form.

Table 3.1 Participant Characteristics

ID		P01	P02	P03	P04
Sex		Male	Male	Male	Male
Age (years)		12	4	10	13
Leg Length (m)		0.81	0.5	0.75	0.85
Diagnosis		Bi-spastic	Bi-spastic	Bi-spastic	Uni-spastic
Side		Left	Left	Right	Left
GMFCS		II	I	II	I
Orthotics		Bilateral AFO-FCs	Bilateral AFO-FCs	Bilateral AFO-FCs	Left lift
Prior Baclofen (mg)*		5 as needed	10 2x/day	10 2x/day	None
SBLTT Only	Weeks	8	10	11	10
	ΔS (mph)	1.5	0.8	1.8	2.3
tSCS+SBLTT	Weeks	11	10	11	9
	ΔS (mph)	1.1	0.9	2.2	1.6
tSCS Amplitude (mA) T11 | L1 Mean (Min, Max)		54 (12, 54) | 40 (15, 40)	55 (20, 60) | 45 (15, 47)	20 (15, 30) | 25 (20, 30)	40 (10, 40) | 30 (20, 30)

*The more-affected side is based on the side with more spasticity at baseline and parent reports. ID = participant identifier; Bi-spastic = bilateral spastic CP; Uni-spastic = unilateral spastic CP; Side = more-affected side; GMFCS = Gross Motor Function Classification System; AFO-FC = ankle foot orthosis footwear combination; ΔS = Change in fast burst SBLTT speed from first to last session, based on the fastest speed at the first and last session. tSCS amplitude applied to T11 = thoracic spinous process 11, L1 = lumbar spinous process 1. *Baclofen use was gradually weened to zero under the guidance of the child's primary care physician ending two weeks prior to enrollment in the study, except P01 who took 5 mg of baclofen once during the SBLTT only phase of the study.*

3.3.3 Outcome measures

Lower limb spasticity and walking distance were the focus of this preliminary study. Outcomes included the Modified Ashworth Scale (MAS), Tardieu Scale, and the 1-minute walk test (1-MWT). MAS was assessed on the hamstrings, quadriceps, gastrocnemius, and soleus muscles bilaterally. MAS scores were converted into an ordinal scale, such that a value of zero indicated no spasticity and a value of five indicated joint rigidity. We also assessed the Tardieu Scale for the hip extensors, knee flexors and extensors, and ankle flexors and extensors as an additional measure of spasticity. Both the MAS and Tardieu scores were averaged across all muscles at each timepoint, with the same assessor each time. Walking capacity in the lab was

measured using the 1-minute walk test (1-MWT), which measures the distance walked in one-minute and is considered a reliable measure of functional ability and walking endurance in ambulatory children with CP [127], [128]. One participant, P01 performed a 6-minute walk test at every time point, before we switched to the 1-MWT to enable work with younger participants (P02-4). The 6-MWT distances for P01 were converted to a 1-minute walking distance by calculating the average distance walked in 1-minute for each assessment.

Biomechanical changes in walking were also assessed at the hip, knee, and ankle joints on each participant's more-affected side. Joint kinematics and muscle activity were quantified during overground walking on a 10-meter walkway. Participants were instructed to walk at a self-selected pace while barefoot for a minimum of 25 steps at each assessment timepoint. Lower extremity motion data were collected using a modified Helen-Hayes marker set [129] and a 10- or 12-camera motion capture system at 120 Hz (Qualisys AB, Gothenburg, SE). Data were processed using custom MATLAB scripts (MathWorks, Natick, MA, USA) and OpenSim v4.3 (Stanford, USA) using a 23 degree-of-freedom model scaled to each individual participant [130], [131]. Across trials, the root-mean-square (RMS) and maximum model error for all markers were below 2 cm and 4 cm, respectively, which align with best practices for model quality [132]. Each joint's dynamic range was calculated as the average change in joint angle across gait cycles, specifically knee and hip extension to examine mechanics related to crouch gait [133].

Electromyography (EMG) data (Delsys Inc, Natick, MA) were synchronously recorded during motion capture trials bilaterally for five muscles: rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), and medial gastrocnemius (MG). Using custom MATLAB scripts, raw EMG signals were high pass filtered (4th order Butterworth; 20 Hz), zero-centered, rectified, and low pass-filtered (4th order Butterworth; 10 Hz). Signals were then

normalized to the 95th percentile of maximum activation across trials for that day and reported as millivolts/millivolts (mV/mV). Integrated muscle activity was defined as the area under the curve for predefined phases of the gait cycle [134]. Co-contraction of antagonistic muscle pairs was defined as the co-contraction index (CCI) calculated as:

$$CCI\,(\%) = {}^{2I_{ant}}\!\Big/\!_{I_{tot}} \times 100, \tag{3.1}$$

where I_{ant} is the antagonistic muscle activity and I_{tot} is the sum of agonist and antagonist EMG activity [135].

Walking capacity and performance were evaluated by lab- and community-based measures. Walking speed (10-meter walk test, 10-MWT), functional mobility (Timed Up and Go, TUG), and dynamic balance (Pediatric Balance Scale, PBS) were evaluated in a lab-setting [136]–[138]. Patient-Reported Outcomes Measurement Information System (PROMIS®) Pediatric Profile-Fatigue short form was used for child-reported level of fatigue for all participants except P02 whose parent completed the parent proxy form due to the child's young age [139].

To quantify community-based walking activity, participants wore a step counter (StepWatch, Modus Health, Edmonds, WA) on their left ankle for seven consecutive days. Data from four weekdays and one weekend day were included for the final analyses. Average daily stride rates were calculated for each participant because evidence shows that high stride rates in natural environments indicate higher participation [36]. To evaluate child and parent perceptions about gait outcomes, we used child and parent-reported questionnaires, the Gait Outcomes Assessment List (GOAL) [140]. Total scores were calculated for each participant and parent. Means and standard deviations were calculated for all outcomes. Hatchfill2 was used in MATLAB to provide color patterns in some figures [141].

3.4 RESULTS

We found that tSCS + SBLTT reduced spasticity with a maintenance of walking function in all participants. Spasticity, measured by MAS, improved by 1.4 ± 0.22 after tSCS + SBLTT compared to 0.43 ± 0.39 after SBLTT only. Average MAS scores remained low for 8-weeks after tSCS + SBLTT but not after SBLTT only compared to pre-intervention scores (Figure 3.2A). Reduced spasticity following tSCS + SBLTT was also indicated by the Tardieu scale. Spasticity reduced by 4.3 ± 3.0 points after SBLTT only and 7.3 ± 4.3 points after tSCS + SBLTT. Reduction in average Tardieu scores nearly sustained through 8-weeks follow-up after tSCS + SBLTT (Figure 3.2B).

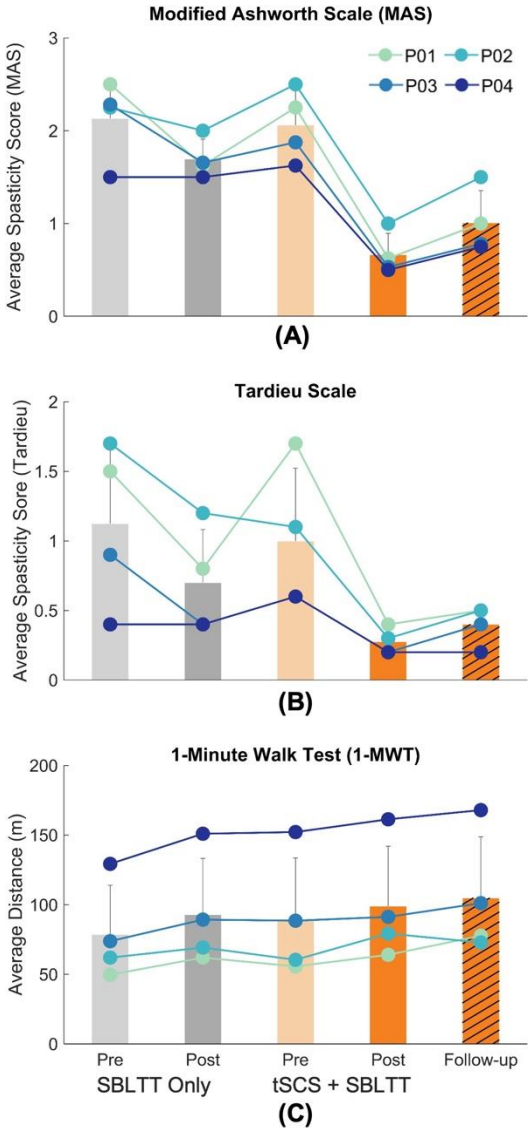

Figure 3.2 Spasticity outcomes of A) Average Modified Ashworth Scale (MAS) for four muscles bilaterally, B) Tardieu Scale, as well as C) walking distance during the 1-minute walk test (1-MWT) for each participant before and after each intervention and after 8-weeks follow-up. SBLTT: Short-burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

The reductions in spasticity of individual muscles were greater across the tSCS + SBLTT intervention compared to SBLTT only (Figure 3.3). The greatest reductions in spasticity during tSCS + SBLTT were observed in the gastrocnemius and soleus muscles (Figure 3.3). These muscles both contribute to ankle plantarflexion, with the gastrocnemius muscle also contributing to knee flexion. Reductions in spasticity were also observed at the hamstrings and quadriceps but were more variable across interventions.

Distance walked during the 1-MWT was maintained throughout both interventions (Figure 3.2C). We observed a small increase of 14 ± 6 meters (m) after SBLTT only and continued increase of 10 ± 7 m after tSCS + SBLTT.

We also documented more joint extension and dynamic range of motion during walking after tSCS + SBLTT compared to after SBLTT only. During SBLTT only, participants had minimal change in hip and knee peak extension by an average of -0.42 ± 7.3° and 2.4 ± 6.6°, respectively. This may have contributed to a change in the overall joint dynamic range of motion during walking after SBLTT only of 2.0 ± 3.5° and -2.4 ± 11.0° for the hip and knee, respectively. In contrast, after tSCS + SBLTT, participants increased peak joint extension during gait, with average improvements of 4.9 ± 7.3° and 6.5 ± 7.7°, driving increases in joint dynamic range of motion of 4.3 ± 2.4° and 3.8 ± 8.7° at the hip and knee, respectively (Figure 3.4A and B). Minimal changes were observed in joint kinematics at the ankle (Figure 3.5).

In addition to changes in joint mechanics during tSCS + SBLTT, all participants maintained or reduced muscle activity in the VM and MG muscles after tSCS + SBLTT. Integrated VM activity during stance increased on average 5.9 ± 12 during SBLTT only and decreased 3.1 ± 2.5 during tSCS + SBLTT. Integrated MG midstance decreased 0.41 ± 1.4 and 1.2 ± 1.2 during SBLTT and tSCS + SBLTT, respectively. This resulted in greater decreases in co-contraction during tSCS + SBLTT compared to SBLTT only between the VM and BF (SBLTT only: 5.6 ± 11%; tSCS + SBLTT: -18 ± 19%) and between the MG and TA (SBLTT only: 0.43 ± 9.4%; tSCS + SBLTT: -7.9 ± 9.7%).

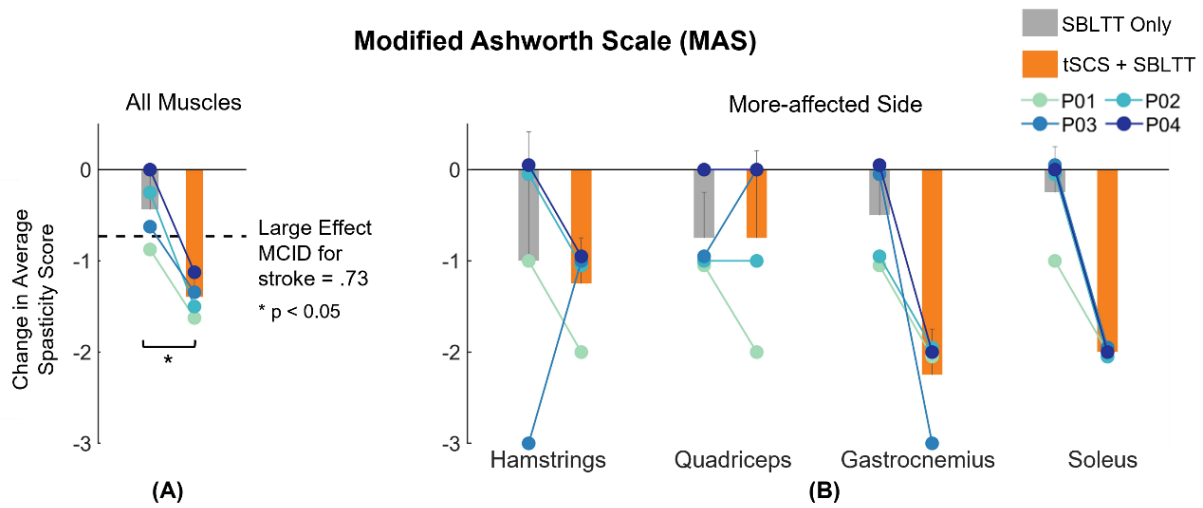

Figure 3.3 Change in muscle spasticity measured using the Modified Ashworth Scale (MAS). A) Results averaged across all muscles bilaterally, were lower after tSCS + SBLTT than SBLTT only. The horizontal dashed line indicates the minimum clinically important difference (MCID) for spasticity reduction in adults post-stroke [142], *as similar values are not available for children with CP. B) Secondary outcomes of individual muscle MAS for the more-affected side of each participant, including the hamstrings, quadriceps, gastrocnemius, and soleus. Larger negative numbers indicate greater reductions, or improvements, in muscle spasticity.*

Participants' walking speed improved during both interventions. Specifically, walking speed, measured via the 10-MWT improved by 0.06 ± 0.10 meters/second (m/s) after SBLTT only and by 0.16 ± 0.25 m/s after tSCS + SBLTT (Figure 3.6A). We measured an increase in community mobility following tSCS + SBLTT. Peak stride rate in the community did not change after SBLTT only but improved by 3.0 ± 4.1 strides/minute after tSCS + SBLTT (Figure 3.6B).

Functional mobility and balance were also assessed in the laboratory. Average time taken to complete TUG reduced by 1.3 ± 1.6 seconds after SBLTT only, and further reduced by 0.4 ± 1.0 seconds after tSCS + SBLTT (Figure 3.7B). Dynamic balance as evaluated by PBS scores improved by 3.7 ± 3.2 points after SBLTT only with continued improvements of 3.7 ± 5.5 points after tSCS + SBLTT (Figure 3.7C).

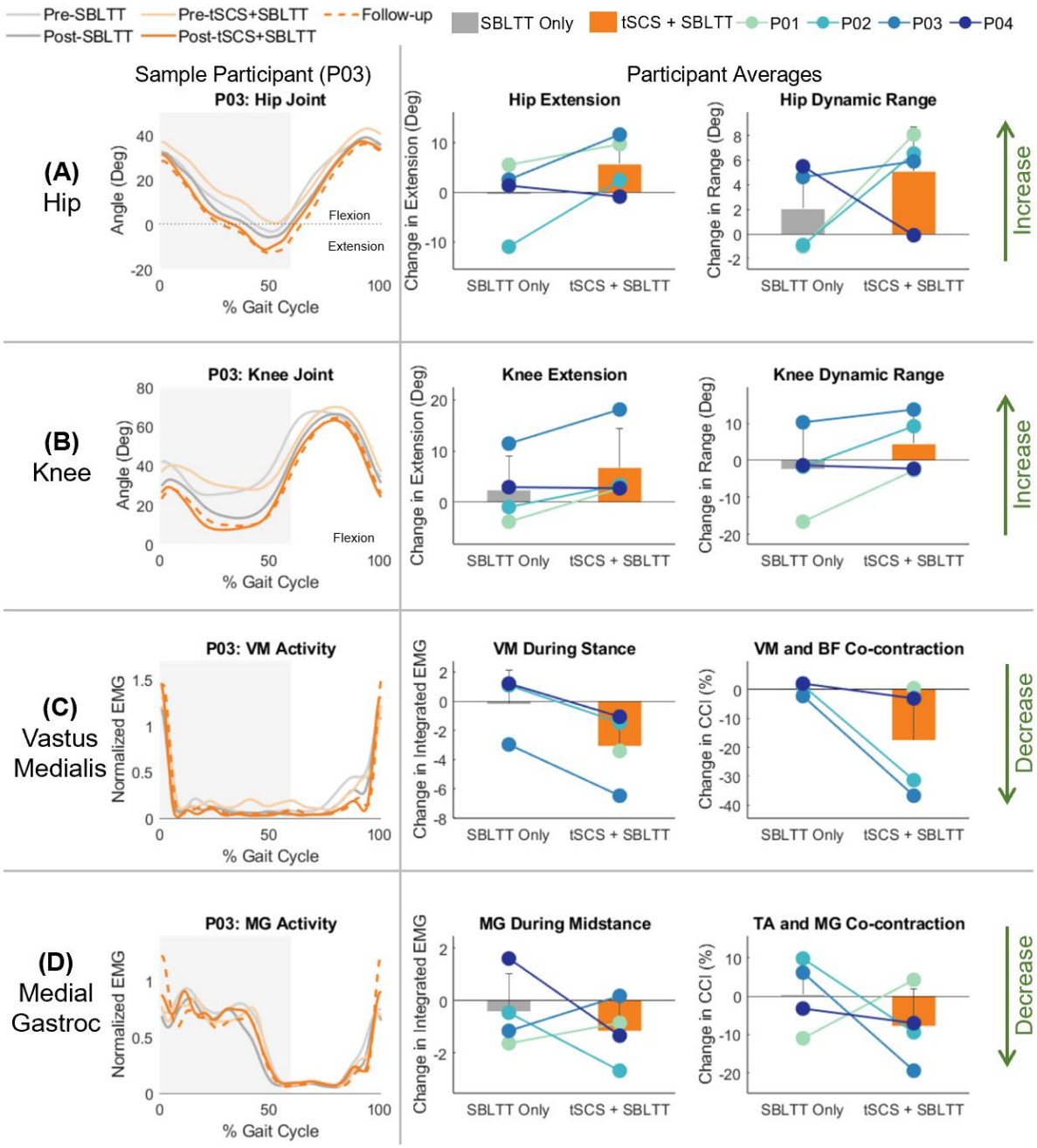

Figure 3.4 Average joint kinematics and muscle activity during barefoot walking at a self-selected speed. The left column shows examples from P03, other columns represent data from all participants as follows. Changes in A) hip and B) knee joint kinematics, C) vastus medialis (VM) activity and co-contraction index (CCI) between the VM and biceps femoris (BF), and D) medial gastrocnemius (MG) activity and CCI between the MG and tibialis anterior (TA). Arrows indicate desired direction of change for each variable, including increased hip/knee extension, increased dynamic range of motion, decreased muscle activity during stance, and decreased co-contraction. Notes: The VM data from P01's baseline visit is missing from (C) due to poor EMG signal during data collection. The sample VM activity from P03 in (C) also has a consistent large artifact at heel strike, likely due to sensor movement.

All participants reported greater reductions in fatigue after tSCS + SBLTT compared to after SBLTT only. Participants reported a 3.8 ± 3.0 point increase in fatigue after SBLTT only, but a 1.0 ± 2.2 point decrease in fatigue after tSCS + SBLTT as captured via the PROMIS® (Figure 3.6C). Child-reported gait outcomes scores reduced by 4.3 ± 5.5 points after SBLTT only and increased by 9.7 ± 8.5 points after tSCS + SBLTT. Parent-reported gait outcomes scores reduced by 1.8 ± 0.96 points after SBLTT only but improved by 3.0 ± 4.1 points after tSCS + SBLTT (Figure 3.8).

Lastly, there were no serious adverse events during the study. The only minor expected event was mild erythema around cathodes that resolved on its own within 15 minutes after stopping the stimulation, which occurred three times for P01.

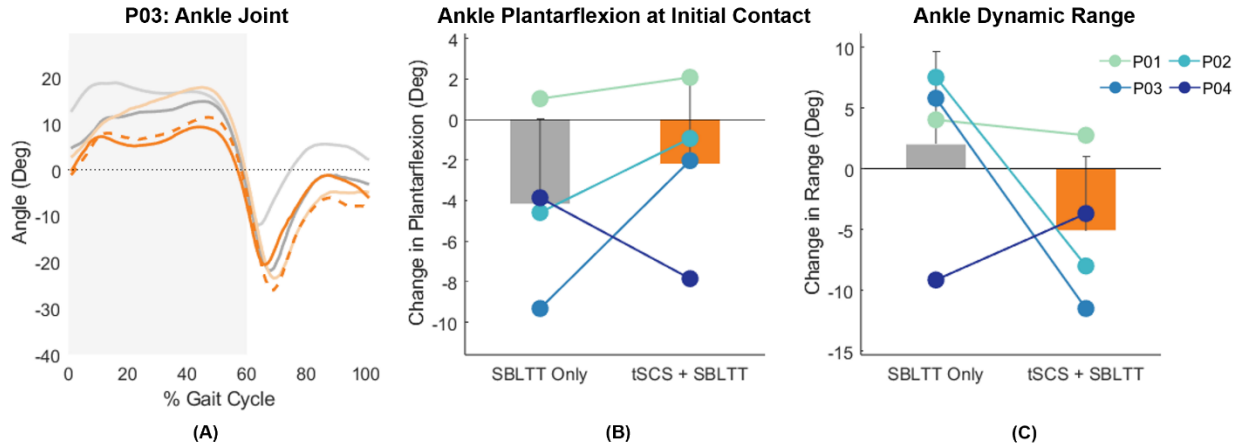

Figure 3.5 Changes in joint kinematics at the ankle showing A) an example trajectory over the gait cycle from P03, B) change in ankle dorsiflexion at initial contact (0-5% of the gait cycle), and C) the dynamic range of the ankle. All measurements were taken during self-selected barefoot walking.

3.5 Discussion

The combination of transcutaneous spinal cord stimulation and SBLTT (tSCS + SBLTT) led to greater improvements in spasticity compared to SBLTT only. tSCS + SBLTT also showed improvements in joint dynamic range with less demand on muscles during walking compared to

SBLTT only. Laboratory assessed walking function was maintained, despite reductions in spasticity, with trends toward more satisfaction with community mobility from children and parents after tSCS + SBLTT compared to SBLTT only. Further, nearly all improvements were retained for at least two months after tSCS + SBLTT and less so in the follow-up after SBLTT only, demonstrating sustained benefits of reduced spasticity and better walking function persist following tSCS + SBLTT for these four children with CP.

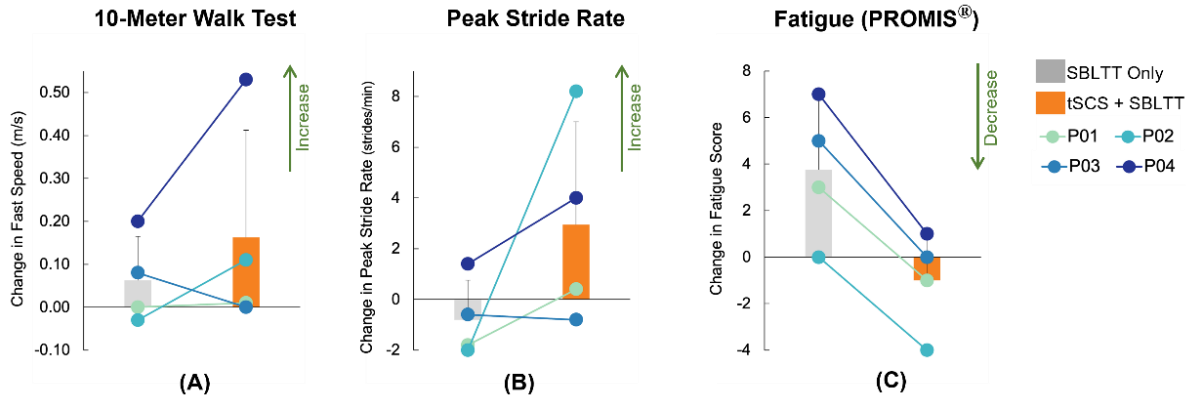

Figure 3.6 Improvements in walking capacity and performance as measured by A) lab-based walking speed via the 10-meter walk test (10MWT), B) community peak stride rate captured via StepWatch device in children's natural environments, and C) reduction in self-reported fatigue scores captured via the Patient-Reported Outcomes Measurement Information System (PROMIS®) Pediatric Profile Fatigue short form. Arrows indicate the desired direction for improved function.

It is important to place the observed changes in spasticity in a clinical context. MAS scores reduced after tSCS + SBLTT more than SBLTT alone. While there is no reported minimum clinically important difference (MCID) for the MAS in children with CP, in adults who had a stroke, however, an average change in lower extremity MAS of 0.73 is considered a large effect MCID [142]. All four children with CP in our study achieved this MCID for reduction in spasticity after tSCS + SBLTT, which was also sustained for at least two months with no further study treatment (Figure 3.3). It is also interesting to note that families anecdotally reported changes in clinical recommendations following participation in the study. For P02, their physician no longer recommended selective dorsal rhizotomy (SDR) and P03 was told they could remain off spasticity

medication for at least another 6 months before reassessment after spasticity reductions observed during the tSCS + SBLTT portion of the study.

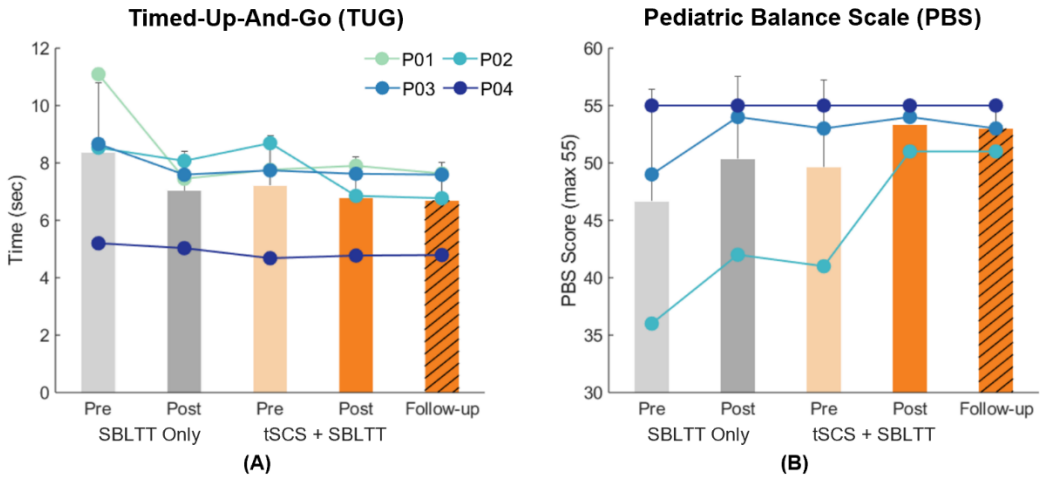

Figure 3.7 A) Time taken to complete Time-Up-And-Go (TUG) reduced for all participants during SBLTT only and was maintained during tSCS + SBLTT. B) All participants improved on the Pediatric Balance Scale (PBS) during both interventions or had reached the ceiling in the assessment.

Common, clinically available treatments of spasticity for children with CP include botulinum toxin type-A (BTA) injections, baclofen, and SDR surgery. BTA injections are applied intramuscularly and reduce muscle activity by blocking acetylcholine release from motor neurons at the neuromuscular junction [56]. BTA injections provide temporary reduction in spasticity, requiring repeated injections that come with negative effects on muscle development and reduced spasticity response on repeated use [56], [125]. Baclofen is a pharmacological intervention option that can be taken orally or delivered via an implanted pump. Baclofen reduces the release of excitatory neurotransmitters in the spinal cord that contribute to spasticity [61].

While these treatments are effective, they have certain limitations that may constrain their use in children. For example, baclofen may result in epilepsy, anxiety, and sleep disorders [143], [144]. SDR is a neurosurgical procedure that permanently transects afferent nerves in the spinal cord after which children require intensive rehabilitation to recover to pre-SDR function.

Considering the side effects that may accompany these treatments, studying new spasticity management methods becomes an important aspect of research inquiry. Our pilot study showed improvements in spasticity following tSCS + SBLTT with no adverse events; therefore, non-invasive spinal cord stimulation warrants further investigation as a management approach for spasticity in children with CP.

Our findings build on prior studies of tSCS showing improved function for children with CP, whereas most prior studies have not evaluated impacts on spasticity [13], [14], [17]. In the one prior study that evaluated spasticity, they reported a reduction in spasticity for four children at GMFCS Level III-V, although the muscles for which spasticity was quantified were not reported. No effect of tSCS on spasticity was reported for the two GMFCS Level I-II children included in the study when tSCS was combined with activity-based neurorehabilitation therapy [15]. This could be because tSCS was applied to the cervical and thoracic spine levels and at lower amplitudes (12-18 mA at C5-6 and 10-16 mA at T11-12) and utilized a different physical therapy compared to the present study. These differences suggest that the type of activity used with tSCS, as well as the stimulation location and amplitude, may influence the efficacy of tSCS in modulating spasticity. This emphasizes the need for future inquiry, with subsequent work required to consider how to optimize physical therapy paired with tSCS to positively impact spasticity, mobility, and daily activities.

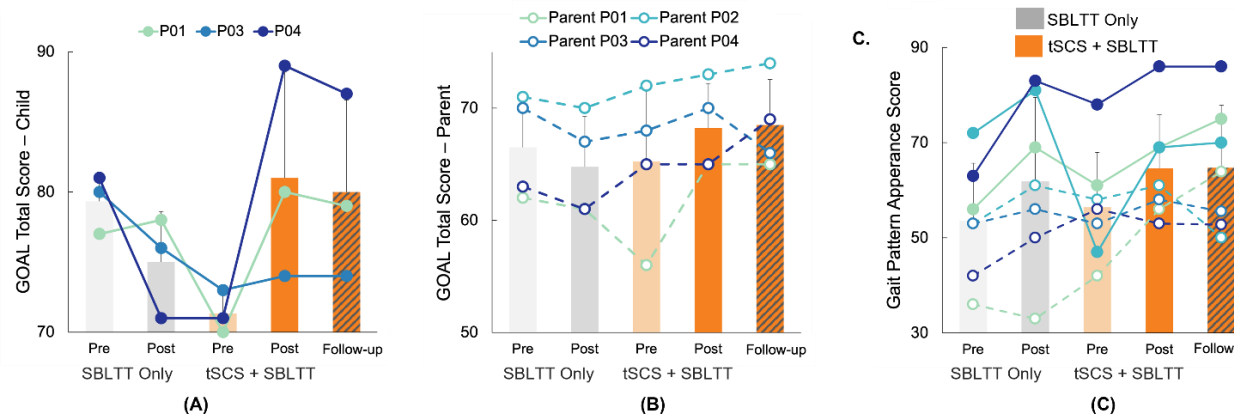

Figure 3.8 A) Child and B) parent-reported total Gait Outcomes Assessment List (GOAL) scores, and C) Child and parent reported Gait Pattern Appearance domain scores. Higher scores indicate better self-reported gait function. Please note that the y-axis does not begin at zero for all GOAL results.

We also observed greater improvements in hip and knee extension after tSCS + SBLTT compared to SBLTT only. Increases in hip and knee extension are characteristics of reductions in crouch gait [145]. Reductions in spasticity at the hamstrings and gastrocnemius may have driven increased knee extension over 24 sessions of tSCS + SBLTT, but further investigation is needed [146].

We also quantified reductions in excessive muscle activity in the vastus medialis during tSCS + SBLTT compared to SBLTT only. Walking with less crouch gait can reduce demand on hip and knee extensors, as we observed here with less hamstring activity, and potentially reduce fatigue [147]. We observed greater self-reported fatigue, after SBLTT only, but not after tSCS + SBLTT. Fatigue in CP is associated with deteriorated walking, especially as children transition into adulthood [148]. Therefore, approaches that reduce fatigue are a high priority for the CP community [149].

Interestingly, minimal changes were observed in ankle joint kinematics, despite large improvements in spasticity at the ankle (Figure 3.3). This may be because all participants wore their community assistive devices during SBLTT, including three participants who wore their

rigid ankle foot orthoses-footwear combination (AFO-FC) that limits movement of the ankle. We chose to use the children's prescribed AFO-FC during SBLTT to maximize transfer to daily activities. The AFO-FCs likely supported the fast-walking speeds achieved during SBLTT but may have also reduced the sensory feedback that tSCS aims to boost during training, and potentially limiting therapeutic effects at the ankle. Evaluating the effects of orthoses on training responses represents an important area for future research.

We also observed some individual improvements in lab-based, community-based and self-reported measures of walking function. All participants increased walking distance during the 1-MWT after SBLTT only and reached at least a medium effect of the MCID, with two participants reaching the large effect MCID. All participants also increased their 1-MWT distance after tSCS + SBLTT, with two participants reaching the large effect MCID [150]. All participants improved their TUG performance time after SBLTT only, with one participant reaching a large effect MCID and another reaching a medium effect MCID. Three of four participants further improved TUG performance time after tSCS + SBLTT, with two participants reaching the large effect MCID [150]. This suggests that both SBLTT only and tSCS + SBLTT improve walking performance in a clinically important way, but only tSCS + SBLTT led to sustained improvements in both spasticity and walking function 8 weeks after the intervention was complete.

Children with CP often have reduced levels of physical activity in daily life and demonstrate less walking intensity compared to typically developing peers [151]. Our early findings suggest that tSCS + SBLTT may facilitate community walking intensity, as shown by higher peak stride rates [80]. Improvements in lab-based measures of walking function provide preliminary evidence on the effects of tSCS + SBLTT on walking capacity in a controlled

environment, while improvements in peak stride rate captured in the community via a StepWatch provide insight into transference to children's day-to-day natural environments.

Positive self-reported changes in gait outcomes captured via the GOAL questionnaires provide a holistic view of participants' and their parents' positive subjective gait-related experiences after tSCS + SBLTT. Both children and parents reported either an increase or a maintenance in achieving walking goals after tSCS + SBLTT. This was driven by improvements in Domain E: Gait Pattern and Appearance. Future work should explore the use of tSCS + SBLTT to understand its implementations and user's perceptions on how they may affect community mobility.

It is also important to establish the underlying neuromechanical mechanisms driving changes for evidence-driven, personalized rehabilitation. By modulating sensorimotor activity, tSCS aims to induce neuroplasticity, or promote a more natural organization of neural pathways, thereby improving sensory integration and motor control [12], [108]. In children with CP whose early brain injury affects both the spinal and supraspinal circuits, [29], [35] disorganization between the supraspinal and the spinal pathways causes inadequate sensorimotor processing [35]. This further leads to a disruption of inhibitory and excitatory inputs, manifesting as spasticity [40] and impacting mobility [152]. We theorize that the combination of tSCS and motor training promotes reorganization of the spinal-supraspinal connectivity by amplifying sensory signals at the level of the spinal cord during functional activities [15], [21]. Motor practice during this amplified state of sensory feedback may result in improved sensorimotor integration at both spinal and supraspinal levels that is maintained for at least several months following treatment [21]. Our findings provide preliminary support for this hypothesis, allowing for simultaneous improvements in how sensory information is integrated both involuntarily

(i.e., spasticity) and voluntarily (i.e., walking). Confirming the underlying neurophysiological effects of neuromodulation represents an exciting avenue for future work.

Despite encouraging findings, there are several limitations to this work. First, the small sample size and variability in ages of four males with spastic CP and GMFCS I-II limits the generalization of results. A second limitation of this study is that the timing over which each intervention was delivered differed slightly due to their family's availability and the COVID-19 pandemic. One participant also completed the majority of SBLTT sessions in an integrated home program with two researchers coming to the home. Nonetheless, the number of therapy sessions was the same between all participants and intervention phases and demonstrates the ability of the intervention to adapt to family needs with the aim of reducing burden on families. Third, we did not restrict the physical therapy that participants may have been receiving outside the study. However, this indicates that even when the interventions are applied in the real-world context of changes to daily life, tSCS + SBLTT consistently resulted in greater improvement in spasticity compared to SBLTT only. Further, we did not measure motor threshold for each participant and thus are unable to report the level of sub-motor threshold stimulation as a percentage of motor threshold. Future work should consider incorporating quantitative methods of measuring motor threshold, such as with electromyography, as an additional method of calibrating the amplitude of stimulation. We also acknowledge that there is a potential for assessor bias, as there was no blinding in the study. Participants were also not blinded to the treatment arms, which may have introduced response bias into more subjective assessments such as GOAL and PROMIS®. Future studies should consider blinding the assessors, especially for subjective measures such as the MAS, and blinding participants to the treatment arms by utilizing sham stimulation. Lastly, the true effect size of tSCS + SBLTT could not be estimated

because SBLTT alone was always delivered first. There may have been an additive effect across interventions that should be controlled in future studies using a randomized study design.

3.6 Conclusion

In this pilot study, we report that the combination of transcutaneous spinal cord stimulation and short-burst interval locomotor treadmill training led to sustained reductions in spasticity for at least 8 weeks in four children with cerebral palsy. During both short-burst interval locomotor treadmill training alone and its combination with stimulation, walking function was maintained despite reductions in spasticity. Children walked with less crouch mechanics, while also reporting improved gait outcomes and reduced fatigue after training with spinal stimulation. Future research should investigate the applicability of these findings to other forms of therapy for children with CP and elucidate the underlying neuromechanics driving improvements. Further studies are needed to quantify how spinal stimulation and physical therapy interventions can be integrated to address the needs and goals of children with CP.

3.7 Acknowledgements

The authors thank the children and their families for the time they dedicated to the research. We also thank Dr. Soshi Samejima, Rich Henderson, and Lauren Bachman for assisting with interventions and assessments, and Avocet Nagle-Christensen for data analysis. Chet Moritz serves as a clinical advisor to the company SpineX, who provided the stimulator for the study.

Chapter 4

EFFECTS OF SPINAL STIMULATION AND SHORT-BURST TREADMILL TRAINING ON GAIT BIOMECHANICS IN CHILDREN WITH CEREBRAL PALSY

In Review Gait & Posture

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4.1 ABSTRACT

Children with cerebral palsy (CP) have an injury to the central nervous system around the time of birth that affects the development of the brain and spinal cord. This injury leads to changes in gait neuromechanics, including muscle activity and joint kinematics. Transcutaneous spinal cord stimulation (tSCS) is a novel neuromodulation technique that may improve movement and coordination in children with CP when paired with targeted physical therapy. The purpose of this study is to quantify how the combination of tSCS and short-burst interval locomotor treadmill training (SBLTT) affect gait neuromechanics in children with CP. Four children with CP (4-13 years old), received 24 sessions each of SBLTT only and SBLTT with tSCS (tSCS+SBLTT). Clinical assessments of spasticity and passive range of motion (PROM), as well as biomechanical assessments of joint kinematics, musculotendon lengths (MTLs), and muscle activity were recorded during overground, barefoot walking. Assessments were taken before, after, and at 8-weeks follow-up. The combination of tSCS+SBLTT led to greater increases in hip and knee extension than SBLTT only for three of the four children. Three children also became more plantarflexed at the ankle during stance after tSCS+SBLTT compared to SBLTT only. While tSCS+SBLTT reduced spasticity, these changes were only weakly correlated with changes in MTLs during gait or PROM, with the largest correlation between change in gastrocnemius operating MTL during fast walking and gastrocnemius spasticity (R^2 = 0.26) and change in plantarflexor PROM and gastrocnemius spasticity (R^2 = 0.23). Children with CP used a more upright, less crouched posture during gait after tSCS+SBLTT. Large reductions in spasticity after tSCS+SBLTT were only weakly correlated with changes in kinematics and PROM. Understanding the mechanisms by which tSCS may affect gait for children with CP is critical to optimize and inform the use of tSCS for clinical care.

4.2 INTRODUCTION

Cerebral palsy (CP) is caused by an injury to the central nervous system around the time of birth that affects the control of movement. This initial injury also leads to secondary effects, such as spasticity, contracture, bone deformities, and shortened musculotendon units that contribute to altered gait mechanics in children with CP [27], [153]. Changes in motor control further contribute to altered coordination and fatiguing gait patterns [154], [155].

Transcutaneous spinal cord stimulation (tSCS) is a novel intervention that may support reorganization of neural pathways to improve movement coordination for children with CP [14], [15], [17]. A single session of tSCS has been shown to improve coordination between the hip and knee during gait and reduce inefficient muscle co-contraction [17]. Prior work has hypothesized that tSCS supports neuroplasticity by inducing reorganization of the central nervous system [21]. Repeated delivery of the combination of tSCS and physical therapy has led to improvements in gross motor function for children with CP [13]–[15]. Understanding the neuromechanical response to therapeutic tSCS is critical in defining the mechanisms by which spinal stimulation may improve gait and function.

Our prior work has shown preliminary evidence that combining tSCS with treadmill training can reduce spasticity while maintaining clinical measures of walking function [23]. We evaluated the combined effects of tSCS with short-burst interval locomotor treadmill training (SBLTT). SBLTT is designed to mimic natural variability of a child's walking pattern, providing intensive walking practice alternating between slow and fast speeds [156]. Prior work has demonstrated how evaluating changes in gait neuromechanics – including outcomes like joint kinematics, muscle activity, or musculotendon lengths (MTLs) can provide key insights into the mechanisms by which interventions like orthopedic surgery [69], [157] or spasticity treatments [158] impact gait and

inform clinical decision-making [159], [160]. Reductions in spasticity, such as those reported after botulinum toxin type-A injections (BoNT-A) or selective dorsal rhizotomy (SDR), may increase passive range of motion (PROM) or increase joint extension and MTLs during gait [161]–[165].

The purpose of this study was to quantify the effects of SBLTT with and without tSCS on gait kinematics, muscle activity, MTLs, and PROM in children with CP and how these changes relate to changes in spasticity. We hypothesized that reductions in spasticity with tSCS+SBLTT would be associated with increases in PROM, greater extension in the hip and knee throughout the gait cycle, reductions in ankle dorsiflexion during stance, and increases in MTLs during gait.

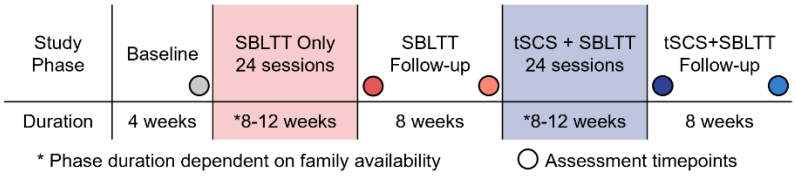
4.3 METHODS

4.3.1 Study Design

This study quantifies gait biomechanics collected during a preliminary investigation [23] of the impacts of SBLTT and tSCS+SBLTT on spasticity and walking. Each participant received 24 sessions of SBLTT first, and then 24 sessions of tSCS+SBLTT, with an 8-week follow-up after each intervention (Figure 4.1). Clinical assessments for PROM and spasticity, as well as gait analysis of kinematics, MTLs, and muscle activity were recorded the week immediately before and after each intervention and at 8-weeks follow-up. All assessment visits were conducted at the University of Washington. This study was approved by the University of Washington Human Subjects Division (IRB identifier: STUDY00008896) and was registered on ClinicalTrials.gov (NCT04467437).

Each training session included a 5 to 15-minute active warm-up either overground or on the treadmill, 30-minutes of SBLTT, and a 5-minute active cool-down. Rest breaks were provided as needed, and participants were encouraged to use handrails for safety. SBLTT was individualized

(A)



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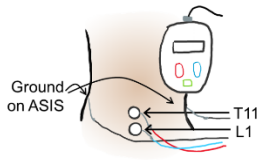

(C)

ID	Sex	Age (years)	Leg Length (m)	Diagnosis	Side	GMFCS	Orthotics	Amplitude (mA) T11	Amplitude (mA) L1
P01	M	12	0.81	Bi-spastic	Left	II	Bilateral AFO-FCs	54 [25-54]	40 [15-40]
P02	M	4	0.50	Bi-spastic	Left	I	Bilateral AFO-FCs	55 [20-60]	45 [15-47]
P03	M	10	0.75	Bi-spastic	Right	II	Bilateral AFO-FCs	20 [15-30]	25 [20-30]
P04	M	13	0.85	Uni-spastic	Left	I	Left lift	40 [10-40]	30 [20-30]

(D)

Figure 4.1 A) Diagram of child walking on treadmill for Short-burst interval locomotor treadmill training (SBLTT). B) Study timeline indicating assessment timepoints before and after each intervention and at 8-weeks follow-up. C) Diagram of investigative spinal cord neuromodulation device (SpineX, Inc.) with stimulating electrodes on the T11 and L1 dorsal spinous processes and two ground electrodes on the anterior superior iliac spine (ASIS). D) Participant information: ID = participant identifier; Bi-spastic = bilateral spastic CP; Uni-spastic = unilateral spastic CP; Side = more-affected side based on the side with more spasticity at baseline and parent reports; GMFCS = Gross Motor Function Classification System Level; The tSCS amplitude applied to T11 = thoracic spinous process 11, L1 = lumbar spinous process with values reported as median [range].

based on baseline overground walking speeds and consisted of 30-second bursts, alternating between walking at a slow and fast pace [80]. The slow pace remained constant between visits, while the fast speed increased based on perceived exertion. During training, all participants wore devices they used during community walking, including ankle foot orthoses footwear combinations and shoe lifts (Figure 4.1D).

During tSCS+SBLTT, the same protocol for SBLTT was followed with the addition of transcutaneous spinal cord stimulation, administered via an investigative spinal cord neuromodulation device (SpineX, Inc.) [17]. Stimulation was applied using adhesive gel electrodes placed just below the T11 and L1 spinous processes using 3.2 cm round electrodes. The ground electrodes were 5.1 x 8.6 cm rectangular electrodes placed over the anterior superior iliac spine (Axelgaard Manufacturing Co., Ltd., USA) (Figure 4.1C). During each visit, stimulation was applied for an average of 56 ± 10 minutes, including all training and rest breaks. Amplitude for the subthreshold

stimulation was determined based on children's self-report of quality of walking, sensation beneath the cathodes, and a physical therapist's clinical observation of gait quality and participant's behavior (Figure 4.1D).

4.3.2 Participants

We enrolled four ambulatory children with spastic CP Gross Motor Function Classification System (GMFCS) Levels I-II [27] who were not regularly taking spasticity medications, did not have history of SDR, and had not undergone a lower extremity surgery or BoNT-A injections in the past year. Four children with CP participated in the study (Figure 4.1D). Two participants, P02 and P03, weaned off their daily use of baclofen three-weeks before starting the study. Another participant, P01 took baclofen as needed prior to the study and took 5 mg once during the SBLTT phase. P04 did not take baclofen prior to or during the study. Children and parents were informed of the study procedures and signed an informed consent and age-appropriate assent forms.

4.3.3 Clinical Assessments

Modified Ashworth Scale (MAS) was used to assess spasticity of the hamstrings, quadriceps, gastrocnemius, and soleus muscles. MAS scores were converted to an ordinal scale such that a value of zero indicates no spasticity and a value of five indicates a rigid joint. Passive range of motion (PROM) in hip flexion, knee flexion and extension, and ankle dorsiflexion and plantarflexion were measured while lying supine [166]. The hip was flexed when measurements were taken at the knee.

4.3.4 Gait Assessment

Sagittal plane joint kinematics and muscle activity were quantified during gait across a 10-meter walkway. Participants walked barefoot at a self-selected pace for a minimum of ten steps on the more-affected side. Lower extremity position data were collected using a modified Helen-Hayes marker set [23] and a 10- or 12-camera motion capture system at 120 Hz (Qualisys AB, Gothenburg,

SE). Electromyography (EMG) data (Delsys Inc, Natick, MA) were synchronously recorded at 2000 Hz during motion capture trials bilaterally for five muscles: rectus femoris (RF), vastus medialis (VM), biceps femoris (BF), tibialis anterior (TA), and medial gastrocnemius (MG). This was repeated at a fast-walking pace for the calculation of MTLs and musculotendon lengthening rates (MTL rates) for all participants, except P01 who did not complete fast walking trials at Baseline. Faster walking speeds can help identify functional limitations, such as whether or not spasticity is impacting MTLs and MTL rate [167], [168].

4.3.5 Data Analysis

Position data were processed using custom MATLAB scripts (MathWorks, Natick, MA), USA) and OpenSim v4.3 (Stanford, USA) using a 23 degree-of-freedom model scaled to each individual participant [130], [131]. Across trials, the root-mean-square (RMS) and maximum model error for all markers were below 2 cm and 4 cm, respectively [132]. After inverse kinematics were calculated in OpenSim, joint kinematics and MTLs were segmented by gait cycle. The change in joint kinematics during each intervention were calculated as the difference of the average kinematic trajectories between the post-SBLTT and Baseline timepoints and the post-tSCS+SBLTT and SBLTT follow-up timepoints. The derivative of MTL with respect to time was used to calculate the MTL rates. All MTLs and MTL rates were normalized to the muscle length, l_{ref} and $\sqrt{\mathrm{g} \cdot l_{ref}}$, respectively, where l_{ref} is the muscle length when the participant stood in an upright posture [168]. Walking speed was calculated from the distance and time traveled of a reflective marker on the left anterior superior iliac spine for each trial and normalized to participant leg lengths as the nondimensional Froude Number [169].

Raw EMG signals were high pass filtered (4th order Butterworth; 20 Hz), zero-centered, rectified, and low pass-filtered (4th order Butterworth; 10 Hz) using custom MATLAB scripts,

Signals were then normalized to the 95th percentile of maximum activation across self-selected walking speed trials for that day and reported as millivolts/millivolts (mV/mV). EMG data were segmented by gait cycle and any steps with an average standard deviation greater than one or with any single data point that exceeded four standard deviations from the mean were removed. Co-contraction of antagonistic muscle pairs was defined as the co-contraction index (CCI) calculated as:

$$CCI\,(\%) = {}^{2I_{ant}}\!/_{I_{tot}} \times 100, \tag{4.1}$$

where I_{ant} is the antagonistic muscle activity and I_{tot} is the sum of agonist and antagonist EMG activity [170]. We also used weighted nonnegative matrix factorization with the Matrix Factorization Toolbox in MATLAB [171] to calculate muscle synergies. The total variance accounted for by one synergy ($tVAF_1$) is reported as a biomarker for motor control in CP [65], with higher $tVAF_1$ values suggesting less refined motor control.

4.3.6 Statistical Analysis

One-dimensional statistical parametric mapping (SPM) was used to assess the difference between study time points for the kinematic trajectories over gait cycles for each individual (www.spdm1d.org in MATLAB). A normality test (spm1d.stats.normality.anova1) was used to determine whether a one-way Analysis of Variance (ANOVA) was performed or if the non-parametric version was used. If significant, post-hoc SPM two-tailed paired t-test, or the nonparametric equivalent, were used to compare changes during each intervention and follow-up relative to the pre-intervention timepoint with Bonferroni corrections for the four tests (alpha = 0.05). We used linear regression to evaluate the relationship between change in PROM, MTL, and MTL rates with spasticity. Each participant was represented in these models with two data points: one from change after SBLTT only and one from the change after tSCS+SBLTT.

4.4 RESULTS

Spasticity, as measured by the MAS, was reduced to a greater extent after tSCS+SBLTT compared to SBLTT only. In addition, reductions in spasticity were sustained for 8 weeks after tSCS+SBLTT, but not after SBLTT only (Table 4.1) [23].

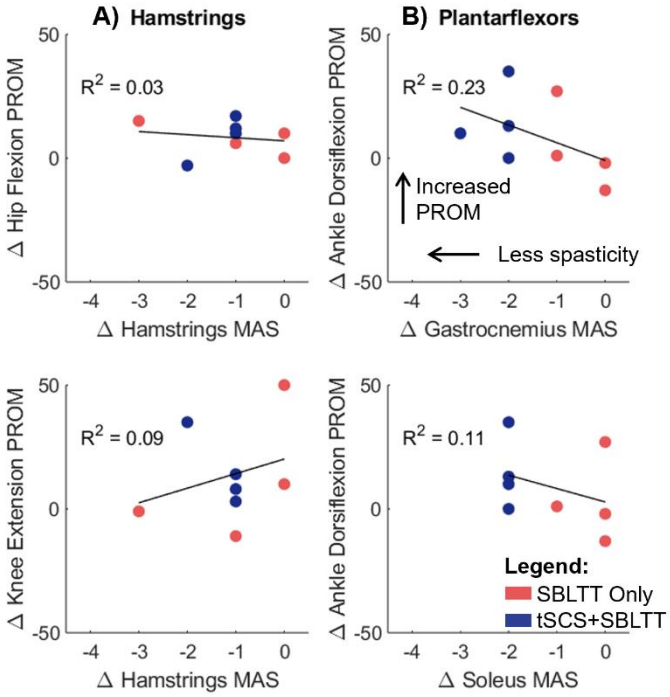

Figure 4.2 Changes in Modified Ashworth Scale (MAS) were only weakly associated with changes in passive range of motion (PROM). Change for each participant after both SBLTT (red) and tSCS+SBLTT (blue) are shown for the (A) hamstrings and (B) plantarflexors.

The PROM across all joints was greater after tSCS+SBLTT compared to SBLTT only by an average of 16° for hip flexion, 11° for knee extension, 9° for knee flexion, 14° for ankle dorsiflexion, and 1° for ankle plantarflexion (Table 4.1). Hip flexion, knee extension, and ankle plantarflexion PROM remained greater at 8 weeks after SBLTT (average >4°), while PROM at all joints except hip flexion remained greater at 8 weeks after tSCS+SBLTT (average >3°). Correlations between changes in PROM and MAS were weak (Figure 4.2). The largest correlation was between change in ankle plantarflexor PROM and gastrocnemius MAS (R^2 = 0.23), with decreases in spasticity after tSCS+SBLTT associated with increased PROM for all four participants (Figure 4.2B).

Table 4.1 Average [Range] spasticity, PROM, and gait measures at each time point.

		Baseline	Post-SBLTT	SBLTT Follow-up	Post-tSCS+SBLTT	tSCS+SBLTT Follow-up
MAS	Quadriceps	1.25 [0-3]	0.50 [0-2]	0.75 [0-2]	0 [0-0]	0 [0-0]
	Hamstrings	1.75 [1-3]	1.75 [0-1]	1.25 [1-2]	0 [0-0]	0.75 [0-1]
	Gastrocnemius	3.50 [3-4]	3.00 [2-4]	3.50 [3-4]	1.25 [1-2]	1.25 [1-2]
	Soleus	3.50 [3-4]	3.25 [3-4]	3.50 [3-4]	1.50 [1-2]	2.00 [1-3]
PROM	Hip Flexion	36 [30-42]	44 [42-45]	40 [30-48]	50 [42-64]	39 [35-42]
	Knee Extension	143 [104-165]	155 [154-155]	149 [127-166]	166 [155-174]	162 [152-167]
	Knee Flexion	132 [121-153]	129 [125-135]	123 [110-133]	138 [130-150]	130 [125-140]
	Ankle Dorsiflexion	66 [50-75]	70 [55-77]	66 [60-80]	84 [73-95]	76 [65-85]
	Ankle Plantarflexion	143 [120-155]	155 [140-268]	149 [130-162]	156 [152-160]	151 [136-174]
Gait Speed	Self-selected Pace	0.45 [0.31-0.52]	0.47 [0.30-0.61]	0.47 [0.36-0.59]	0.49 [0.41-0.58]	0.49 [0.39-0.61]
	Fast Pace	*0.63 [0.53-0.76]	0.64 [0.50-0.91]	0.67 [0.54-0.84]	0.65 [0.44-0.89]	0.71 [0.51-0.93]
Joint Kinematics	Peak Hip Extension	4 [-5-16]	4 [-8-17]	4 [0-16]	10 [3-15]	12 [7-19]
	Minimum Knee Flexion	22 [18-25]	20 [13-29]	24 [19-30]	16 [7-24]	14 [9-21]
CCI (%)	Proximal Muscles	62 [52-68]	67 [53-86]	73 [63-81]	55 [37-81]	58 [36-75]
	Distal Muscles	57 [34-77]	57 [44-74]	67 [62-74]	60 [43-79]	63 [52-85]
Motor Control	$tVAF_1$	*0.77 [0.72-0.87]	0.82 [0.71-0.93]	0.82 [0.74-0.92]	0.82 [0.73-0.92]	0.82 [0.77-0.89]

*MAS: Modified Ashworth Scale; PROM: passive range of motion with measurements at the knee taken while the hip is flexed; CCI: Co-contraction Index; Motor Control as measured by the total variance accounted for in one muscle synergy ($tVAF_1$) on participants' more-affected side, dimensionless gait speed normalized to leg length, and peak extension during gait. *P01 is not included in the baseline fast walking speed or $tVAF_1$.*

Self-selected gait speed increased throughout the study, with an average increase of 0.02 m/s after both SBLTT only and tSCS+SBLTT (Table 4.1). Changes in joint kinematics during gait varied between participants, but all participants had the greatest knee and hip extension post-tSCS+SBLTT or at tSCS+SBLTT follow-up (Figure 4.3-Figure 4.6). Three participants increased their hip extension throughout the gait cycle after tSCS+SBLTT compared to changes after SBLTT only. All participants had a greater increase in knee extension during stance after tSCS+SBLTT compared to after SBLTT only (Figure 4.7). Knee extension during swing increased after SBLTT only for three participants but increased after tSCS+SBLTT for all four participants. Three participants were more plantarflexed at the ankle during stance after tSCS+SBLTT, with their greatest ankle plantarflexion during push-off at the tSCS+SBLTT follow-up. The participant who initially walked in equinus-crouch became more dorsiflexed after tSCS+SBLTT (Figure 4.7; Figure 4.4).

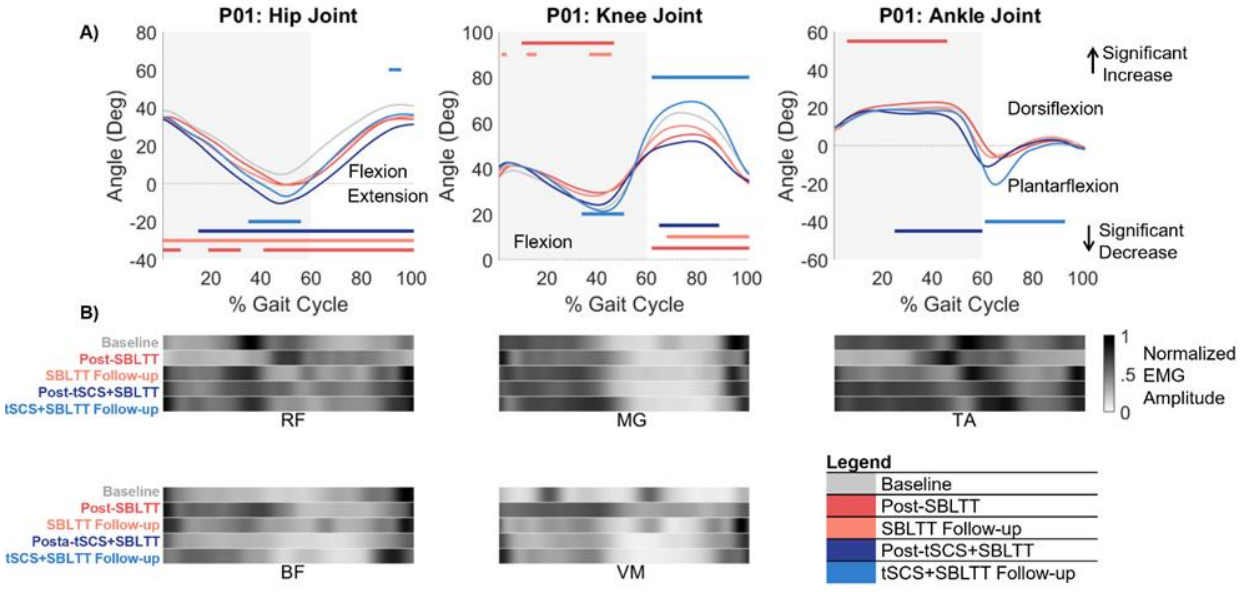

Figure 4.3 P01's more-affected side. A) Sagittal-plane hip, knee, and ankle kinematics over the gait cycle. Horizontal colored lines indicate where there were significant changes in kinematics over each phase of the study based on statistical parametric mapping ($p<0.05$). Lines on top indicate locations of significant increases, while lines on the bottom indicate points of significant decreases. B) Normalized EMG amplitude during gait for the lower extremity muscles.

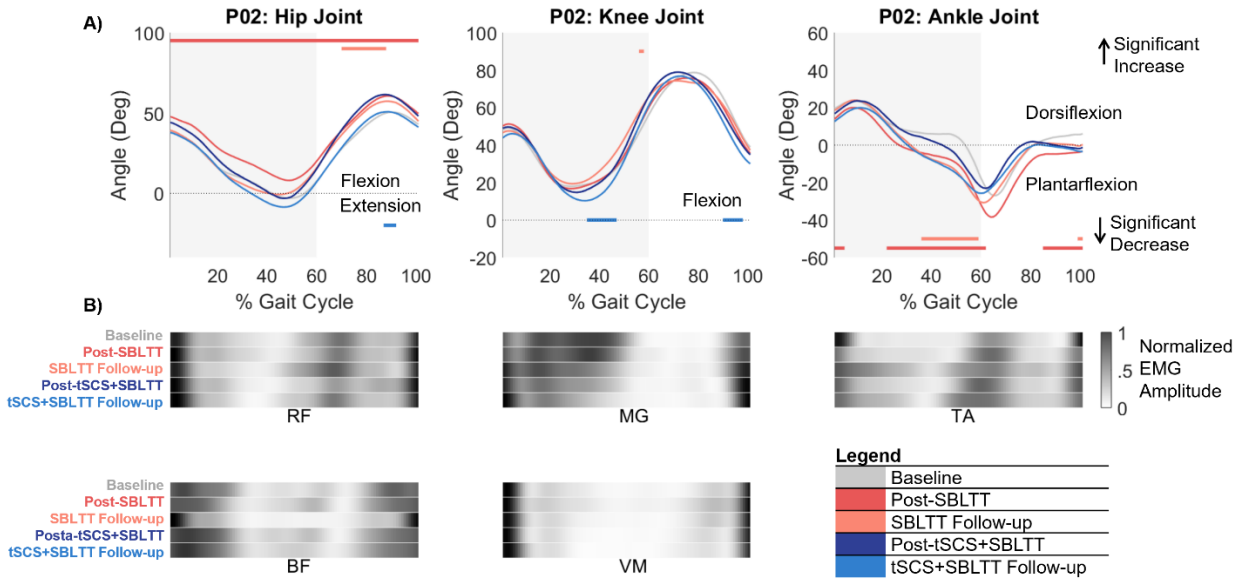

Figure 4.4 P02's more-affected side. A) Sagittal-plane hip, knee, and ankle kinematics over the gait cycle. Horizontal colored lines indicate where there were significant changes in kinematics over each phase of the study based on statistical parametric mapping ($p<0.05$). Lines on top indicate locations of significant increases, while lines on the bottom indicate points of significant decreases. B) Normalized EMG amplitude during gait for the lower extremity muscles.

Despite increases in joint extension, there were minimal changes in the operating lengths of biarticular muscles at self-selected or fast gait speeds. We observed an average increase of 3.0% of the reference length and 0.13 nondimensional (n.d.) in MTL and MTL rate, respectively, across muscles during SBLTT only and an average increase of 2.5% of the reference length and .0014 n.d. in MTL and MTL rate, respectively, during tSCS +SBLTT. Changes in MTLs were only weakly correlated with changes in spasticity at self-selected speeds ($R^2 < 0.18$, Figure 4.8). At fast speeds, decreased gastrocnemius spasticity was associated with increased MTL ($R^2 = 0.26$, Figure 4.8). There were no correlations between changes in spasticity and changes in MTL rate at either speed ($R^2 < 0.02$).

Changes in the timing and magnitude of muscle activations led to less co-contraction after tSCS+SBLTT compared to after SBLTT only (Table 4.1). The proximal muscles, vastus medialis and biceps femoris, had a 5% increase in CCI after SBLTT only and an 18% decrease in CCI after

tSCS+SBLTT. The distal muscles, tibialis anterior and gastrocnemius, had a 0% change in CCI after SBLTT only and a 7% decrease in CCI after tSCS+SBLTT. Motor control during gait, as measured from muscle synergies, decreased slightly after SBLTT only and remained the same after tSCS+SBLTT (Table 4.1).

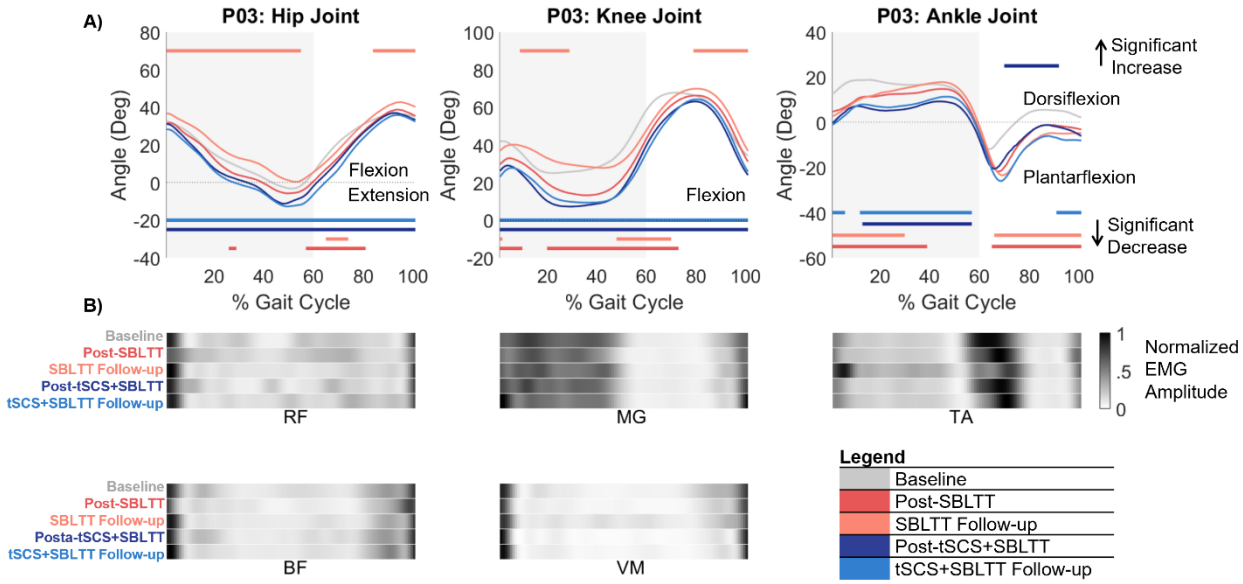

Figure 4.5 P03's more-affected side kinematics and muscle activity. A) Sagittal-plane hip, knee, and ankle kinematics over the gait cycle. Horizontal colored lines indicate where there were significant changes in kinematics over each phase of the study based on statistical parametric mapping ($p<0.05$). Lines on top indicate locations of significant increases, while lines on the bottom indicate points of significant decreases. B) Normalized EMG amplitude during gait for the rectus femoris (RF), biceps femoris (BF), medial gastrocnemius (MG), vastus medialis (VM), and tibialis anterior (TA).

4.5 Discussion

We hypothesized that reductions in spasticity after tSCS+SBLTT would correspond to changes in joint kinematics and muscle activity during gait for children with CP. The combination of tSCS+SBLTT led to more hip and knee extension and thereby a more upright, less crouch position during walking. This new extended position may reduce demand on muscles, such as the reductions in antagonistic muscle co-contraction that we observed after tSCS+SBLTT, and potentially reduce muscle fatigue in CP [172], [173], such as the reductions in antagonistic muscle

co-contraction that we observed after tSCS+SBLTT. Correlations between change in spasticity during each intervention and operating MTLs, MTL rates, and PROM were generally weak.

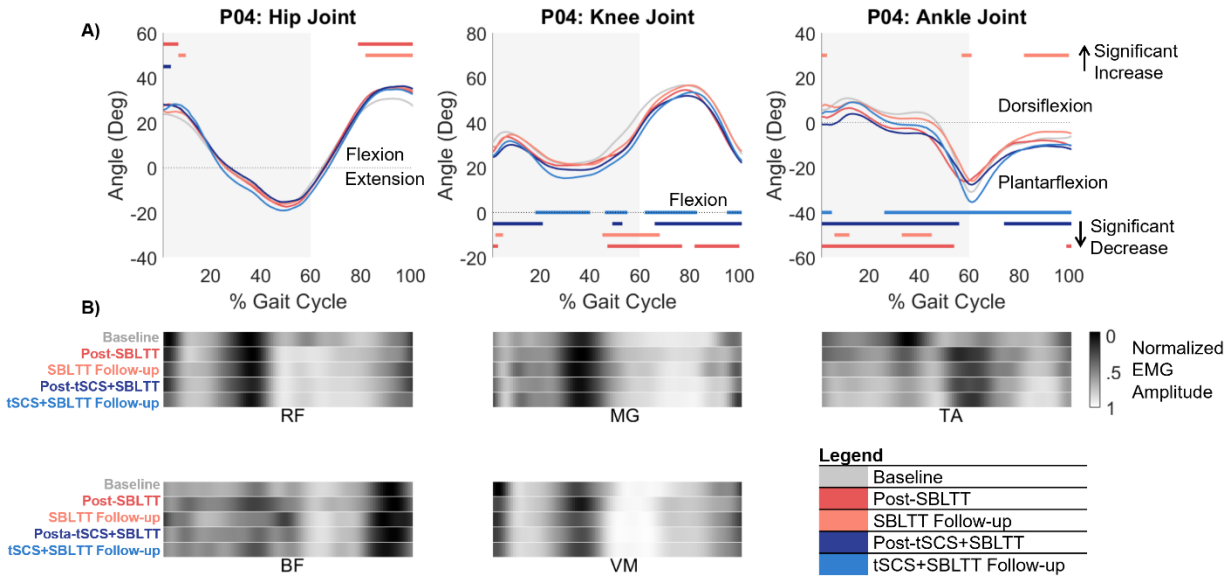

Figure 4.6 P04's more-affected side. A) Sagittal-plane hip, knee, and ankle kinematics over the gait cycle. Horizontal colored lines indicate where there were significant changes in kinematics over each phase of the study based on statistical parametric mapping ($p<0.05$). Lines on top indicate locations of significant increases, while lines on the bottom indicate points of significant decreases. B) Normalized EMG amplitude during gait for the lower extremity muscles.

Like many children with CP, our participants exhibited characteristics of crouch gait at baseline with excessive knee flexion during stance and reduced hip extension, with one participant (P02) in equinus-crouch [46], [172], [174]. All participants exhibited their greatest knee extension during stance at the post-tSCS+SBLTT or tSCS+SBLTT follow-up timepoints. These results suggest that the addition of tSCS+SBLTT may support changes in muscle activity, such as co-contraction and spasticity, that can enable greater knee extension and less fatiguing gait patterns [116], [175] (Table 4.1). Two participants exhibited the greatest shifts in joint kinematics at the tSCS+SBLTT follow-up. While this may be due to continuing effects of the intervention, other environmental factors also likely played a role. For example, P01 started attending in-person school again after pandemic closures between the post-tSCS+SBLTT and the tSCS+SBLTT

follow-up timepoint. His increase in daily walking activity may have further contributed to the positive changes in gait observed after the final non-intervention period [176].

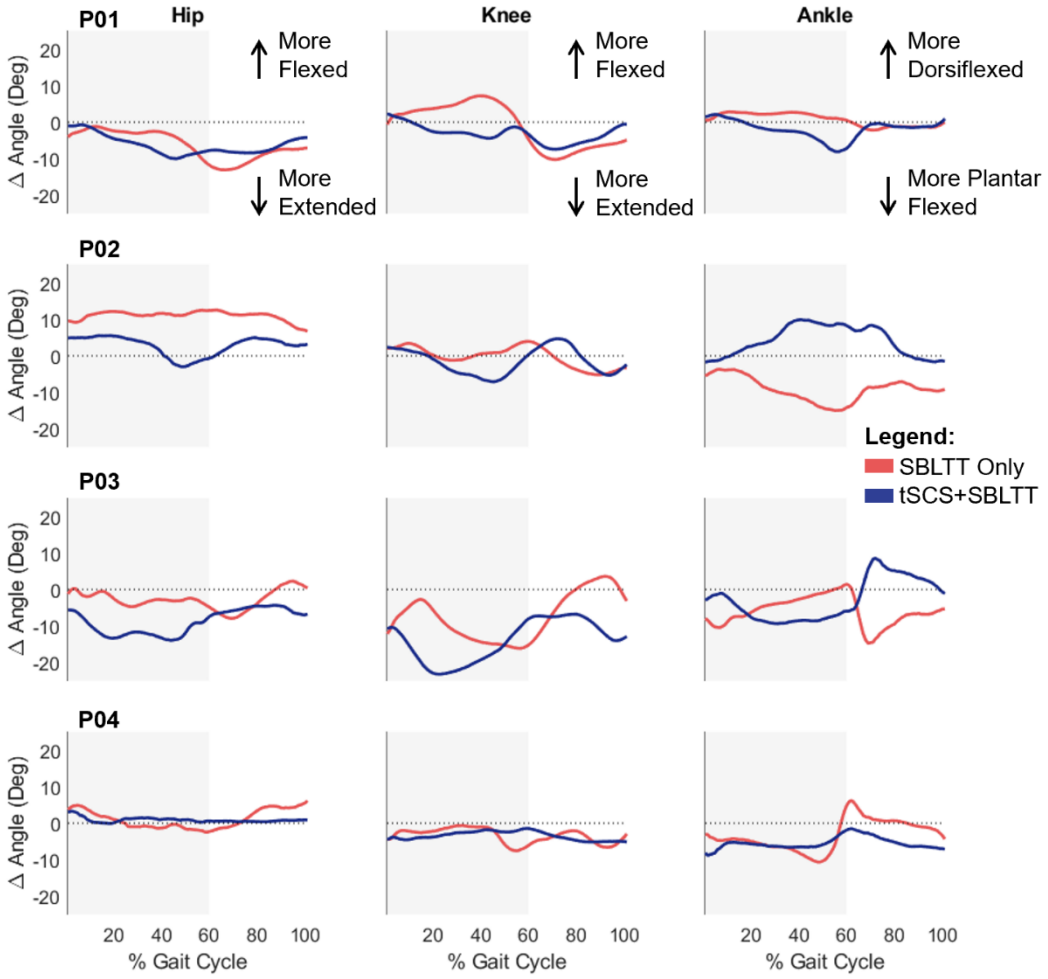

Figure 4.7 Change in the sagittal-plane joint kinematics over the gait cycle for the hip, knee, and ankle after SBLTT only (red) and tSCS+SBLTT (blue) for each participant. Positive values for the hip and knee indicate a more flexed position while negative values indicate a more extended position. A positive value for the ankle indicates a more dorsiflexed position and a negative value indicates a more plantarflexed position. The grey box on each figure indicates the stance phase of the gait cycle.

Previous work has shown that spasticity may be one factor contributing to decreased musculotendon operating lengths and rates during gait for children with CP [161], [167], [168]. Van der Krogt et al. 2009 reported that hamstring and plantarflexor MTLs were 3-5% of the reference length shorter, and MTL rates of approximately 0.03 n.d. slower, for children with high spasticity and contracture compared to typically developing peers [167], [168]. Another group

reported that BoNT-A injections increased rectus femoris MTL by 5 mm and MTL rate by 0.2 m/s on the more spastic side [162]. We observed changes of similar magnitude, although only gastrocnemius MTL, not MTL rate, had a moderate correlation with decreased spasticity (Figure 4.8).

Children with spasticity also have reductions in PROM that can be alleviated with spasticity treatments [177]. Carraro et al., 2014 reported that SDR significantly increased knee extension 13° and foot dorsiflexion 6° [163]. Choi et al., 2016 reported that BoNT-A injections significantly increased ankle range of motion 4° up to 4-months after injection [164]. We observed increases in range of motion and reductions in spasticity of comparable magnitudes. Correlations between PROM and MAS, however, were weak with the greatest correlation between PROM and MAS for the gastrocnemius ($R^2 = 0.23$). This may be the strongest correlation because the positioning of the leg for PROM and MAS were identical, unlike other muscle groups.

Clinically available treatments for spasticity may improve range of motion, but they have minimal or even detrimental effects on motor control [65]. Prior studies of muscle synergies reported a reduction in motor control complexity after SDR and BoNT-A injections (i.e., increase in $tVAF_1$), suggesting that spasticity was masquerading as more complex muscle activity for children with CP. Our observation that $tVAF_1$ stayed consistent during tSCS+SBLTT, despite significant reductions in spasticity, may suggest that tSCS+SBLTT may have positive effects on motor control during gait relative to other approaches for spasticity management.

As a preliminary study with four children with CP, this study has limited generalizability across the highly heterogeneous CP population. Rather, this study provides initial insight into how the addition of spinal stimulation and changes in spasticity may impact gait. We saw that responses varied between individuals and likely depend on factors that should be considered in future studies such as age, baseline function, stimulation intensity, and engagement during sessions. All analyses were performed on overground walking at self-selected or fast pace. There may be small effects of gait speed on outcomes like kinematics or MTLs when participants were instructed to walk at self-selected speed. However, average change in self-selected gait speed across timepoints was minimal (Table 4.1). Our participants had moderate spasticity comparable to children seeking spasticity care in clinical settings [163], [164]. Several participants reached the lowest MAS scores, such that further potential effects on spasticity could not be quantified with MAS alone. Using instrumented spasticity tests may further elucidate the interplay between spasticity and gait biomechanics [178].

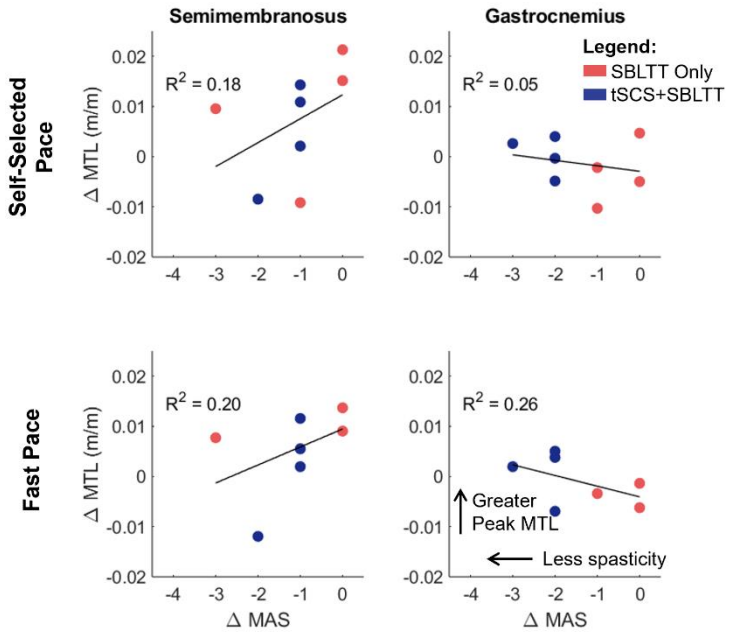

Figure 4.8 Linear regression comparing changes in operating musculotendon length (MTL) during self-selected and fast walking to changes in MAS for the semitendinosus and gastrocnemius muscles on the more affected side. MTLs are normalized to the muscle length when the participant is standing in an upright posture. Note: Fast pace is missing the ΔSBLTT data point for P01 because his fast speed was not recorded at baseline.

The combination of tSCS and SBLTT resulted in reduction in spasticity, as well as changes in passive range of motion and joint kinematics during barefoot, overground walking in four

children with CP. Future work should consider the neuromuscular factors leading to changes in joint movement, both passively and during walking, to further understand the mechanisms behind how tSCS can be optimized for children with CP. Non-invasive neuromodulation has the potential to decrease spasticity and improve walking in children with CP when combined with treadmill training.

4.6 Acknowledgement

The authors thank the children and their families for the time they dedicated to the research. We also thank Dr. Soshi Samejima, Rich Henderson, and Lauren Bachman for assisting with interventions and assessments, and Avocet Nagle-Christensen for assisting with data analysis.

4.7 Conflict of Interest Statement

Chet T. Moritz serves as a clinical advisor to the company SpineX, who provided the stimulator for the study. SpineX also licensed IP generated by the team at the University of Washington, Chet T. Moritz, Katherine M. Steele, Siddhi R. Shrivastav, and Charlotte D. Caskey.

Chapter 5

EFFECTS OF INTERVAL TREADMILL TRAINING ON SPATIOTEMPORAL PARAMETERS IN CHILDREN WITH CEREBRAL PALSY: A MACHINE LEARNING APPROACH

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5.1 ABSTRACT

Quantifying individualized rehabilitation responses and optimizing therapy for each person is challenging. For interventions like treadmill training, there are multiple parameters, such as speed or incline, that can be adjusted throughout sessions. This study evaluates if causal modeling and Bayesian Additive Regression Trees (BART) can be used to accurately track the direct effects of treadmill training on gait. We developed a Directed Acyclic Graph (DAG) to specify the assumed relationship between training input parameters and spatiotemporal outcomes during Short Burst Locomotor Treadmill Training (SBLTT), a therapy designed specifically for children with cerebral palsy (CP). We evaluated outcomes after 24 sessions of SBLTT for simulated datasets of 150 virtual participants and experimental data from four children with CP, ages 4-13 years old. Individual BART models were created from treadmill data of each step. Simulated datasets demonstrated that BART could accurately identify specified responses to training, including strong correlations for step length progression ($R^2 = 0.73$) and plateaus ($R^2 = 0.87$). Model fit was stronger for participants with less step-to-step variability but did not impact model accuracy. For experimental data, participants' step lengths increased by 26±13% after 24 sessions. Using BART to control for speed or incline, we found that step length increased for three participants (direct effect: 13.5±4.5%), while one participant decreased step length (-11.6%). SBLTT had minimal effects on step length asymmetry and step width. Tools such as BART can leverage step-by-step data collected during gait training to monitor progression, optimize rehabilitation protocols, and understand the causal mechanisms driving individual responses.

5.2 INTRODUCTION

A fundamental challenge in gait rehabilitation is quantifying the direct effect of an intervention on targeted outcomes. For example, children with cerebral palsy (CP) often undergo

treadmill training focused on increasing walking speed and step length. In treadmill training, therapists must determine several parameters, such as the duration of training, speed, and incline to optimize therapeutic outcomes. Determining how to adjust these parameters across and within sessions is challenging both for researchers improving protocol design and for clinicians providing individualized rehabilitative care. For children with CP, improving step length is often a goal of gait training to increase joint range of motion and reduce energetic costs. However, since step length is also modulated with treadmill speed and incline, isolating the direct effects of training on step length is limited with traditional methods. Quantifying the direct effect of an intervention on step length is important for understanding therapeutic effectiveness without confounding variables present as an underlying cause of change.

Causal inference and machine learning can help address these limitations by quantifying the direct effect of training parameters on rehabilitation responses. Directed Acyclic Graphs (DAGs) can be used to graphically model the assumed relationship between training parameters and gait outcomes [118], [179]. Traditional methods that quantify pre-post effects do not differentiate between direct and indirect (*i.e.*, mediated) relationships between a variable and outcome across sessions. Alternatively, a DAG can help determine the adjustment set needed to quantify direct effects, or the effect of a treatment on the outcome while controlling for intermediaries that may bias outcomes.

Machine learning provides promising new methods to understand and inform rehabilitation. For treadmill training, a large amount of data can be collected about each step from the treadmills or wearable devices, but this data is rarely used to evaluate training protocols. Leveraging this data collected during treadmill training may enable individualized models to capture direct effects of training on a targeted outcome. Specifically, Bayesian Additive Regression Tree (BART) models

have emerged as a favorable statistical method for handling the nonlinear, interacting effects inherent in gait [117], [180], [181]. BART is a “sum of trees” regression method capable of modeling relationships between exposure and response variables with low levels of bias and variance [182]. Prior research has leveraged DAGs and BART to understand the biomechanical factors that influence elevated energetic costs in CP and to evaluate factors driving treatment outcomes, such as response to orthopedic surgery and ankle exoskeleton assistance [116]–[119]. However, these methods have used population-based models and have not been extended to quantify individual responses.

The purpose of this study was to quantify the accuracy of BART to evaluate changes in gait with treadmill training, using both simulated and experimental datasets. Specifically, we designed BART models to quantify changes in step length with short-burst interval locomotor treadmill training (SBLTT), a training protocol developed for children with CP that has been shown to improve walking speed, endurance, and community mobility [80]. We hypothesized that BART would be able to accurately predict responses from simulated datasets of SBLTT, including correctly identifying the rate at which step length changes between sessions and points of nonlinearity. Further, from experimental data, we hypothesized that SBLTT would have a direct effect on increasing step length.

5.3 Methods

5.3.1 Modeling Framework

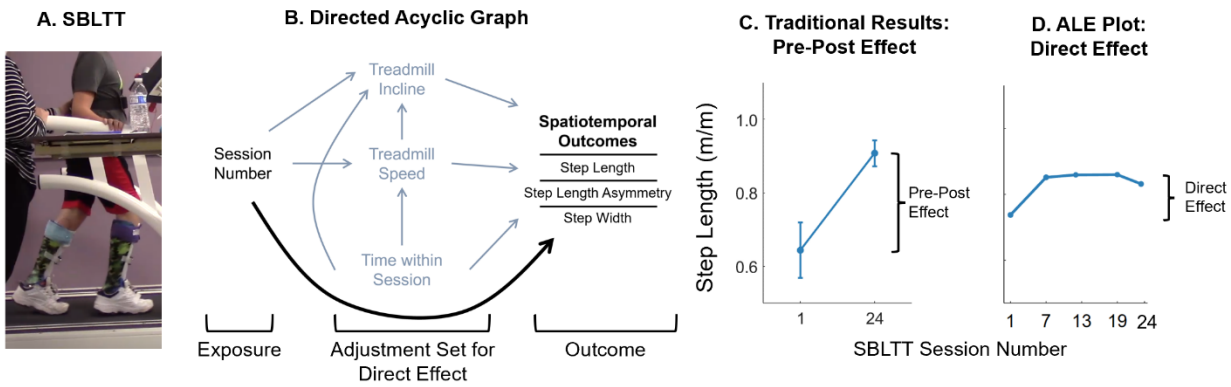
To evaluate whether causal modeling and machine learning can capture individual responses to treadmill training, we first developed a modeling framework to specify the relationship between SBLTT and spatiotemporal outcomes. The SBLTT protocol consists of 30-second bursts, alternating between slow and fast speeds to mimic the natural variability children experience in

daily life. Initial slow and fast speeds are selected based on each individual's self-selected and fast 10-meter overground walking speeds, respectively [183]. The slow speed is kept constant across sessions, while the fast speed is increased based on self-reported and clinician-perceived exertion per a predetermined protocol within and across sessions [184]. If the speed is increased to the point that a participant begins to run, the incline of the treadmill is increased in 1% increments until walking is maintained.

We built a DAG based on the parameters that can be adjusted during SBLTT and are assumed to influence gait outcomes, including treadmill speed, incline, and time within session (Figure 5.1B). This DAG was developed to capture the effect of session number (exposure) on spatiotemporal outcomes (*i.e.*, step length, step length asymmetry, step width) following the guidelines for DAG development [185], [186].

The adjustment set determined from a DAG can be used with any modeling method to account for intermediaries that can induce bias or confounding. For this study, we selected BART because it has demonstrated superior performance in accurately identifying causal effects in complex, simulated datasets relative to other machine learning methods [181]. We created individualized BART models for each participant (simulated and experimental) and each spatiotemporal outcome (Figure 5.1E). The input to the BART model consisted of a large r x p data frame with r rows corresponding to each step recorded on the treadmill and p parameters consisting of the exposure, outcome, and adjustment set. BART models were generated using 10-fold cross-validation for hyperparameter tuning in RStudio (R Version 4.1.3; *bartMachine* package) [187]. For replicability, we set the seed of each model to 18. We used R^2 as a measure of model fit, with an $R^2 = 1$ indicating the BART model fully captured step-to-step variability across sessions.

Accumulated local effect (ALE) plots were used to evaluate the direct effect of each input variable on each spatiotemporal outcome [188]. For each input variable, ALE plots were created using a bootstrapping procedure (n=3), wherein a sample of 75% of the total data were used to generate a series of ALE plots from which the average (± standard deviation) trend was generated (*ALEPlot* package) [189]. These data were binned into evenly space increments as a smoothing procedure. The direct effect of each input variable on the response variable was quantified as the absolute difference between the 10^{th}-90^{th} percentile of the outcome for each ALE plot [119] (Figure 5.1D). These direct effects calculated from ALE plots were compared to the pre-post effects, that are traditionally evaluated in rehabilitation research. The pre-post effects were calculated using the first and last training visit and did not include any adjustment for changes in factors like speed or incline across sessions (Figure 5.1C).



E. BART input and response variables for each of the three spatiotemporal outcomes.

Outcome	**Description**
Step length	Anterior-posterior distance between the center of pressure at the initial point of contact of subsequent foot strikes in meters normalized to leg length (m/m)
Step Length Asymmetry	Percent difference in consecutive left and right step lengths, defined using the Asymmetry Index (% ASI) (Eqn. 1)
Step width	Medial-lateral distance between the center of pressure at the initial point of contact of subsequent foot strikes in meters normalized to leg length (m/m)
Exposure	**Description**
Session Number	Numerical value from 1-24
Adjustment Set	**Description**
Time within Session	Numerical value from 0-30 indicating time since start of SBLTT in minutes
Treadmill Speed	Numerical value of the treadmill speed normalized to leg length and reported as the Froude number
Treadmill Incline	Percentage from 0-2 indicating the percentage incline of the treadmill

Figure 5.1 A) Step length and width were recorded during sessions of Short-burst Interval Locomotor Treadmill Training (SBLTT) using a pressure-instrumented treadmill. B) A Directed Acyclic Graph (DAG) describing the assumed causal relationship between session number (exposure) and spatiotemporal parameters (outcomes). Spatiotemporal outcomes included step length, step length asymmetry, and step width. The adjustment set for direct effects (black arrow) includes time in session, treadmill speed, treadmill incline, and side of the body. No adjustment set is needed when calculating pre-post effects. C) The pre-post effect of SBLTT on spatiotemporal outcomes were calculated using the first and lasts training visit. D) A Bayesian Additive Regression Tree (BART) model was generated for each participant and outcome and used to quantify the direct effect of the input parameters on each spatiotemporal outcome. The direct effect was calculated as the change in outcome from Accumulated Local Effects (ALE) plot for each model input. E) BART input and response variables for each of the spatiotemporal models. This is consistent across the spatiotemporal outcomes, with the addition of including side of the body for separate steps in the width and length calculations.

5.3.2 Simulated Data

To evaluate the accuracy of BART in quantifying changes in spatiotemporal outcomes across sessions, we generated datasets of virtual participants using custom MATLAB scripts. Each virtual participant was assigned an initial walking speed, step length, step length variability, and rate at which step length increased with training progression. These variables were selected randomly from normal distributions based on experimental data. To evaluate the prediction accuracy of BART, we fit a linear model to the specified and predicted rate of change of step

length across sessions, calculated from the average ALE slope. We report the linear fit (R^2) between specified and predicted values as a measure of model accuracy which converged by 150 participants.

Given the high step-to-step variability expected in children with neurological injury receiving physical therapy [190], we quantified the impact of step-to-step variability on BART model fit, we used the same process described above, but varied the standard deviation of each virtual participant's step length variability, ranging 1-45 millimeters (mm). We used linear regression to evaluate whether step-to-step variability was associated with BART model fit (R^2). Similarly, we evaluated the impact of step-to-step variability on BART model accuracy by evaluating the relationship between each virtual participant's specified variability and the error in predicted step length change across session numbers. Given the importance of understanding if someone is no longer responding to an intervention, we also measured the accuracy of BART to detect plateaus in step length progression. We randomly specified a plateau at the 1st, 6th, 12th, 18th, or 24th visit, while the relationships between other variables were unchanged. We compared the association between the specified and predicted plateau points using linear regression. ALE plot slope less than 0.6 mm/session was considered a plateau point to account for variability in the data.

5.3.3 Experimental Data

To evaluate the use of BART with experimental data, we collected spatiotemporal data on four children with CP undergoing 24 sessions of SBLTT (Table 5.1). This study was approved by the University of Washington Institutional Review Board (STUDY00008896) and was registered as ClinicalTrials.gov #NCT04467437. Each training session included a 5–15-minute active warm-up either overground or on the treadmill, 30-minutes of SBLTT, and a 5-minute active cool-down.

Table 5.1 Participant Characteristics

Participant Identifier	Sex	Age (years)	Leg Length (m)	Diagnosis	More-affected side	GMFCS Level	Assistive Devices
P01	M	12	0.81	Spastic diplegia	Left	II	Bilateral AFO-FC
P02	M	4	0.50	Spastic diplegia	Left	I	Bilateral AFO-FC
P03	M	10	0.75	Spastic diplegia	Right	II	Bilateral AFO-FC
P04	M	13	0.85	Spastic hemiplegia	Left	I	Left lift

The more-affected side is based on the side with more spasticity at baseline and parent reports. GMFCS = Gross Motor Function Classification System; AFO-FC = ankle foot orthoses footwear combination

Rest breaks were provided as needed, and participants were encouraged to use handrails for safety. During training, all participants wore the orthoses that they used during community walking, including ankle foot orthoses footwear combination (AFO-FC) and shoe lifts (Table 5.1).

To evaluate step-by-step responses, plantar pressure data were collected during five of the SBLTT training sessions using a pressure-instrumented treadmill (h/p/cosmos, Zebris Medical GmbH, Isny, Germany; Figure 5.1A). Pressure data were collected at 300 Hz through the Noraxon MyoPressure Software MR3 (Noraxon U.S.A., Inc., Scottsdale, AZ, USA). MR3 performed automatic step detection, which was confirmed by a researcher. We focused our analyses on three spatiotemporal outcomes: step length, step length asymmetry, and step width. Only the fast speed bursts were used in the analysis as the fast speeds progressed during training to maintain an appropriate exertion level, making them the primary point of interest. Step length was defined as the anterior-posterior distance between the center of pressure at the initial point of contact of subsequent foot strikes. Step length asymmetry was calculated using the asymmetry index (ASI) and represented as a percent difference of consecutive steps [191]:

$$ASI = \frac{2(LA-MA)}{(LA+MA)} \times 100 \quad (1)$$

where LA and MA are the less-affected and more-affected, sides, respectively. Step width was defined as the medial-lateral distance between the center of pressure at the initial point of contact of subsequent foot strikes. All spatiotemporal parameters were calculated with custom scripts in MATLAB (Mathworks, Natick, MA, USA) from the MR3 center of pressure at initial contact for all left and right steps. Step length, step width, and speed were normalized to each participant's leg length, with speed reported as the Froude number [192], and BART models were generated for each participant and spatiotemporal outcome separately. In the step length and width BART models, we further classified steps as either the more- or less-effected side in the data frame, defined by parent reports or level of spasticity as assessed by a physical therapist.

5.4 RESULTS

5.4.1 Simulated Data

Evaluation of 150 virtual participants demonstrated that BART could accurately identify specified changes in step length across sessions. The specified and predicted step length progression with SBLTT were correlated across virtual participants (R^2 = 0.73; Figure 5.2A). Greater step-to-step variability reduced BART model fit (R^2 = 0.70, Figure 5.2B). However, the magnitude of step-to-step variability in a virtual participant's data had no relationship with BART prediction accuracy (R^2 = 0.01, Figure 5.2C). When step length progression was set to plateau, BART models were also able to identify specified plateau points (R^2 = 0.87; Figure 5.2D).

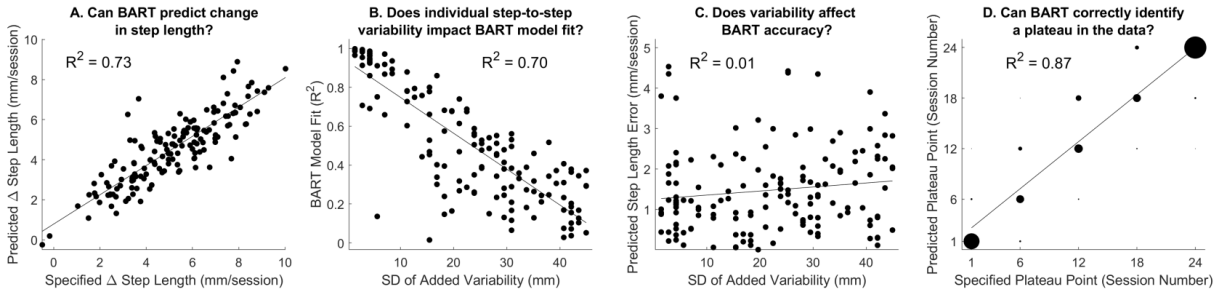


Figure 5.2 Results from in silico methods: A) Specified and predicted change in step length between sessions (mm/session) for virtual participants were highly correlated, R^2 = 0.73. B) Increasing step-to-step variability of virtual participants decreased the variance explained by BART models, R^2 = 0.70. C) Increasing step-to-step variability did not affect the accuracy of BART, R^2 = 0.01. D) When change in step length was halted after a specified session – defined as the plateau point – the BART models of virtual participants accurately identified the plateau point, R^2 = 0.87. Given the overlap in points for identifying plateaus, the size of each data point corresponds to the number of virtual participants in that bin.

5.4.2 Impact of SBLTT on Step Length

SBLTT had a positive pre-post effect on step length, as participants increased step length during fast speed bursts by 26 ± 13% from the first to last SBLTT session (Figure 5.3A). This was paralleled by a 55 ± 24 % increase in treadmill speed (Froude number: +0.20 ± 0.067). Evaluating the direct effects of SBLTT on step length with BART indicated that three participants increased step length by an average of 13.5 ± 4.5% after controlling for all other variables in the DAG (direct effect: 0.11 ± 0.035 m/m; Figure 5.3B and D). The individualized BART models predicted step length with high model fit ($0.77 < R^2 < 0.94$) for these three participants (Figure 5.3C). For the remaining four-year-old participant (P02), step length decreased by 11.4% (direct effect: 0.098 m/m). However, BART model fit was also much lower for P02 (R^2 = 0.21), potentially reflecting P02's greater step-to-step variability (P01: 19 mm; P02: 62 mm; P03: 30 mm; P04: 42 mm).

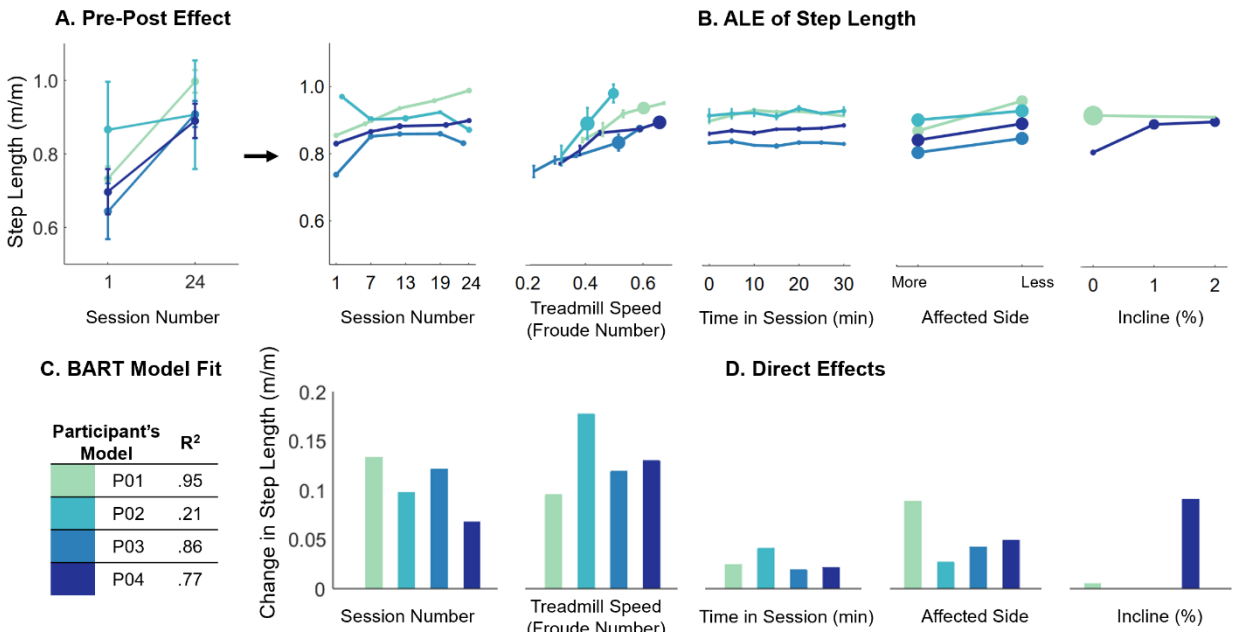


Figure 5.3 A) Pre-post effect of SBLTT on step length for the more affected side. B) BART results quantify direct effects of SBLTT on step length. Accumulated Local Effects (ALE) plots for each input variable show the effect of that variable on step length including session number, treadmill speed (Froude number), time within session, side, and treadmill incline. The size of the data point on each ALE plot depicts the relative number of data points in each bin. C) BART model fit (R^2) for each participant. D) Direct effects of each input variable on the response variable, step length, calculated from the change in the ALE plots in B).

5.4.3 Impact of SBLTT on Step Length Asymmetry

The pre-post and direct effects of SBLTT on step length Asymmetry Index (ASI) were minimal. The pre-post effects indicated that ASI increased by 2.1 ± 4.3 percentage points with SBLTT during the fast speed bursts (Figure 5.4A). All participants favored a longer step on the less-affected side. The BART models had poor to moderate fit for ASI ($0.08 < R^2 < 0.64$; Figure 5.4C). SBLTT session number had a direct effect of decreasing ASI for two participants (P01: 5.6 percentage points; P04: 10 percentage points) and increasing ASI for two participants (P02: 5.5 percentage points; P03: 4.5 percentage points; Figure 5.4B and D). Time within session had a small effect on ASI for the diplegic participants (direct effect < 3.0 percentage points), but the hemiplegic participant (P04) consistently became more asymmetric during the time in session (direct effect = 5.2 percentage points).

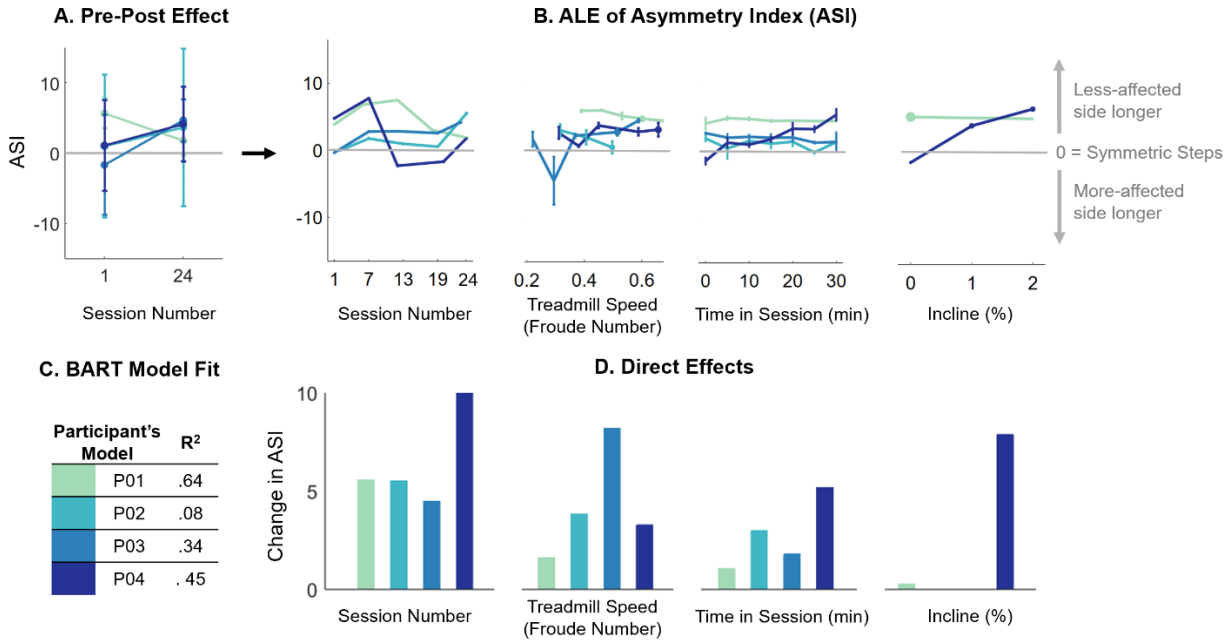


Figure 5.4 A) Pre-post effect of SBLTT on step length Asymmetry Index (ASI). B) BART results quantify direct effects of SBLTT on ASI. ALE plots for each input variable show the effect of that variable on ASI including session number, time within session, treadmill speed (Froude number), and treadmill incline. The size of the data point on each ALE plot depicts the relative number of data points in each bin. C) BART model fit (R^2) for each participant. D) Direct effects of each input variable on the response variable, ASI, calculated from the change in the ALE plots in B).

5.4.4 Impact of SBLTT on Step Width

Minimal changes were also observed in step width after SBLTT. The pre-post effects were highly variable between participants with an average increase in step width of 2.2 ± 23% (Figure 5.5A). BART models had poor to moderate fit for explaining step width variability ($0.06 < R^2 < 0.63$; Figure 5.5C). SBLTT session number had a direct effect of increasing step width for two participants (P02: 11%; P03: 29%) and decreasing step width for two participants (P01: 56%; P04: 30%; Figure 5.5B and D). The direct effects from BART indicated minimal effects of treadmill speed, treadmill incline, or time in session on step width (direct effect < 0.03 m/m).

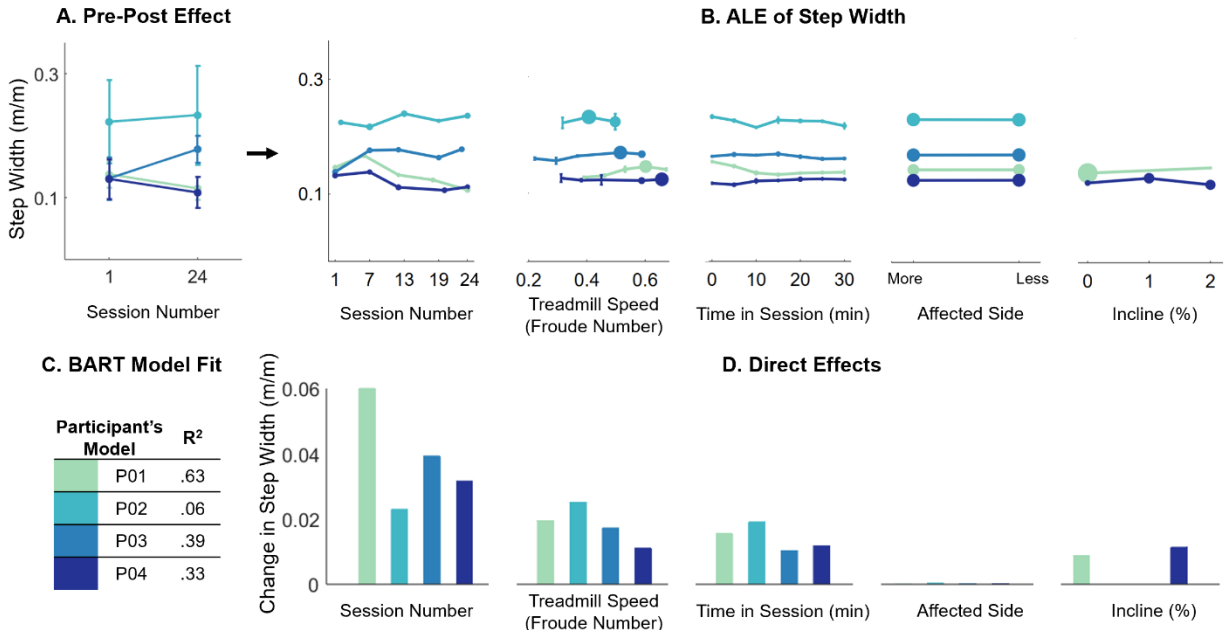


Figure 5.5 A) Pre-post effect of SBLTT on step width when the more affected side is ahead. B) BART results quantify direct effects of SBLTT on step width. ALE plots for each input variable show the effect of that variable on step width including session number, treadmill speed (Froude number), time within session, side, and treadmill incline. The size of the data point on each ALE plot depicts the relative number of data points in each bin. C) BART model fit (R^2) for each participant. D) Direct effects of each input variable on the response variable, step width, calculated from the change in the ALE plots in B).

5.5 Discussion

We demonstrated that BART accurately quantified the direct effects of treadmill training on step length using simulated datasets that mimicked the step-to-step variability and anticipated training progression. We further demonstrated the feasibility of BART to track individual treatment progression of SBLTT for four children with CP. While all four participants showed an increase in step length between the first and last session (pre-post effect), after controlling for other factors, SBLTT only had a direct effect on increasing step lengths in three participants. In contrast, there were minimal pre-post or direct effects of SBLTT on step length asymmetry or step width.

With simulated data, BART was able to accurately predict the direct effect of SBLTT session number on step length and identify points of nonlinearity (*i.e.*, plateau points) with an $R^2 > 0.7$ in both scenarios. While this indicates there may remain some error in the predicted model, the strong

relationship suggests BART may be useful to track progression across rehabilitation sessions. There is also no indication of bias in BART accuracy at different magnitude of rate of change of step length with session (*i.e.* BART did not consistently over or underestimate rate of change). Since many populations, including children with CP, often demonstrate greater step-to-step variability [190], it was encouraging that the simulated dataset demonstrated that greater step-to-step variability did not impact the accuracy of the BART model prediction. This aligns with prior work indicating that BART was not misled by pure noise in a dataset [182]. These characteristics make BART ideal for modeling rehabilitation progression and understanding how to design protocols to maximize benefit.

In prior work, BART has been used for population-level models for CP, similar to prior machine learning approaches commonly used in biomechanics [193]. This was the first paper to demonstrate the potential impact of extending these methods to individual models. We demonstrated BART had high accuracy at modeling individual, nonlinear rehabilitation progression by leveraging step-by-step data collected during a training activity. Prior work has also emphasized the importance of individualized models in rehabilitation [194]. For example, individual musculoskeletal models provide insight into how impairments like contracture or weakness influence gait [195], [196]. Combining individualized musculoskeletal models with the approaches presented in this paper may provide further opportunities to understand the mechanisms driving responses to rehabilitation, determine how to tune rehabilitation parameters, and develop effective rehabilitation protocols. The DAG we used to inform our BART model focused on the effects of treadmill training parameters on step length, but it remains unclear by what mechanisms SBLTT improved step length (*i.e.* changes in motor control, spasticity, or strength).

We chose to focus on step length in this initial analysis because children with CP often exhibit reduced step length and speed compared to nondisabled peers [197]–[199]. For the three participants who demonstrated that SBLTT had a direct effect on increasing step length, these improvements in step length surpassed the minimum clinically important difference with a large effect whether considering the pre-post or direct effects (6.7 % and 6.3 % for GMFCS I and II, respectively) [200]. These results are also similar to changes in overground step length at a self-selected speed for children with CP undergoing a combined stretch and strength program [201].

Children with CP often exhibit increased step length asymmetry and width compared to nondisabled peers, indicators of reduced walking stability [197], [198], [202]. SBLTT had minimal effects on step length asymmetry and step width. During all SBLTT sessions, children were encouraged to use the handrails for safety, which likely influenced these spatiotemporal outcomes as the handrail offered an additional point of contact for stability [203]. While we aimed to keep handrail usage consistent across sessions, we did not record whether usage differed within or between participants. Recording and including this information in the DAG and BART model could be used to understand the effects of constraints like handrails or bodyweight support systems on outcomes. Additional variables that my need to be included to improve the model fit for asymmetry and step width may include perceived fatigue, audiovisual input (*e.g.*, verbal cues), or trunk movement [204], [205].

For the 4-year-old participant (P02), all models had poor fit ($R^2 < 0.21$). Our simulated analysis demonstrated this is likely driven by the highly variable gait pattern, which is characteristic of this age due to developing motor and postural control [206], [207]. However, the simulated results also indicated that increased variability did not negatively affect accuracy (Figure 5.2C). Additional factors may need to be included in the DAG and BART model for younger

children to understand the causes of the step-to-step variability, such as measures of neuromuscular activity or engagement.

Causal modeling and machine learning, especially methods that are nonlinear and interpretable like BART, are useful tools to parse complex, individualized rehabilitation responses. A limitation in these approaches is that they require a large amount of data – in this case, many steps monitored during treadmill training. Applying these methods to other environments may require the use of emergent techniques in wearable sensing to acquire large datasets. With only four participants, the resulting findings on SBLTT are not expected to be generalizable to other children with CP. However, they provide a framework for more detailed evaluations of individual intervention progression for heterogeneous populations like CP. Further, we only recorded 5 of 24 sessions to track progression, but quantifying spatiotemporal outcomes at each session may give more detailed insight into treatment progression. Despite these limitations, this work shows the potential efficacy of using BART for quantifying individual responses to interventions and for tracking training-specific parameters that may be used for determining optimal protocols. In addition to treadmill training, this may be useful for other rehabilitation methods, such as determining the level of assistance in an exoskeleton or the stimulation parameters for brain or spinal cord stimulation.

Using BART, we quantified step-by-step personalized response to SBLTT and demonstrated that BART can be used to track the direct effect of SBLTT on spatiotemporal outcomes in CP. Even after controlling for increases in walking speed and other training parameters, three of the participants demonstrated a direct effect of SBLTT training on increasing step length. These methods can be expanded to evaluate other training programs and people seeking rehabilitative care. Further, using wearable sensors or video-based techniques could offer additional insights into

step-by-step changes in gait during rehabilitation [208]–[210]. Pairing these rich data sources with causal modeling and machine learning paradigms can support rehabilitation researchers and clinicians in optimizing protocols and delivering more individualized care to enhance mobility.

5.6 Conflict of Interest Statement

The authors have no conflicts of interest for the present work.

Chapter 6

EFFECTIVENESS OF SPINAL STIMULATION FOR REDUCING FATIGUE WHEN TRAINING WITH A RESISTIVE ANKLE EXOSKELETON FOR CHILDREN WITH CEREBRAL PALSY

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6.1 ABSTRACT

The muscles in children with cerebral palsy (CP) fatigue faster than the general population, a likely contributor to reports of increased fatigue in daily life. Considering fatigue during rehabilitation is important for children with CP to prevent over-exertion of muscles that can limit motor learning. Transcutaneous spinal cord stimulation (tSCS) may improve coordination of movement in children with CP and reduce fatigue during training, potentially amplifying neuroplasticity in response to rehabilitation interventions. The purpose of this study was to quantify how tSCS and a resistive ankle exoskeleton (Exo) affect muscle fatigue during treadmill training in children with CP? Nine children with CP (4-14 years old) participated in four 20-minute sessions of walking with (1) no devices, (2) tSCS only, (3) Exo only, and (4) tSCS+Exo. Plantarflexion maximum voluntary contraction (MVC) was performed before and after the walking tasks. During the MVC and first 5-minutes of the walking tasks, electromyography (EMG) data from the soleus was recorded. Soleus amplitude and median frequency (MDF) were used as biomarkers for muscle fatigue, with a simultaneous increase in amplitude and decrease in MDF indicative of muscle fatigue. Participants fatigued during all four walking tasks, but the rate of fatigue was greatest during the Exo only condition where EMG amplitude increased 83% at a rate of 13% per minute, while MDF decreased 19% at a rate of 5% per minute. There were minimal changes in MDF during other tasks, but soleus EMG amplitude increased during the tSCS+Exo condition. The use of tSCS with Exo reduced muscle fatigue compared to training with the Exo alone, even with increasing plantarflexor engagement. Walking with amplified sensory feedback from either tSCS or Exo may improve muscle coordination when performing the MVC task despite fatigue in muscles during the walking task. Considering how muscles fatigue during training can help optimize the treatment plan by determining treatment length for optimal motor learning.

6.2 INTRODUCTION

Among ambulatory people with cerebral palsy (CP), one of the main complaints is fatigue in daily life. Individuals with CP use 2-3x the energy of nondisabled peers to walk [52]–[54]. Fatigue limits mobility for both children and adults with CP, affecting their ability to perform tasks of daily living and interact with peers [5], [211], [212].

Muscle fatigue is defined as a reduction in force output [213], [214]. Prior to an observable decrease in force output, there are myoelectric manifestations of muscle fatigue. This includes a decrease in the conduction velocity of muscle fibers, which can be quantified as a simultaneous decrease in the frequency and increase in amplitude of electromyographic (EMG) recordings [215]. When performing repetitive tasks, such as walking, the muscles of children with CP fatigue faster than their peers [154], [216], [217]. Changes in muscle properties and reductions in the ability to activate all available muscle fibers may make children with CP more likely to rely on weaker, high-endurance muscle fibers compared to peers [218].

Considering muscle fatigue is important when developing rehabilitation interventions. Over exertion of muscles that results in fatigue during a training session has been shown to reduce motor learning and performance [219], [220]. When the same training is performed with rest breaks to prevent over-exertion, the nervous system is more adaptable to learning new information, a process known as neuroplasticity [220]. Neuroplasticity is key for children with CP who are learning new tasks during therapy. Despite knowing the importance of muscle fatigue on motor learning, fatigue is not often quantified during the development or evaluation of rehabilitation interventions for children with CP. Understanding fatigue during training can provide useful information for determining appropriate session length and optimizing the level of exertion or challenge during an intervention.

Neuromodulation, or the electrical modulation of neural activity, during therapy may be a viable tool for reducing muscle fatigue and improving performance. Transcutaneous spinal cord stimulation (tSCS) has been used alongside physical therapy for children with CP and led to reductions in muscle co-contraction, increases in gross motor function, reductions in muscle spasticity, and improvements in joint extension and dynamic range of motion during walking [13]–[15], [17], [23]. A single session of tSCS has been shown to reduce muscle co-contraction, a fatiguing characteristic of walking often seen in children with CP, and improve coordination between hip and knee motion during gait [17]. This suggests that tSCS may be able to reduce demand on muscles during therapy, thus improving conditions for neuroplasticity and enhancing treatment effects.

The goal of this study was to quantify muscle fatigue before, during, and after 20-minutes of gait training with and without tSCS in nine children with CP. Specifically, we evaluated walking on a treadmill both with and without a resistive ankle exoskeleton designed specifically for children with CP to engage the plantarflexors. We hypothesized that walking with a resistive ankle exoskeleton would produce greater fatigue than walking without the exoskeleton and that tSCS would reduce fatigue during and after walking.

6.3 METHODS

6.3.1 Participants

Nine individuals with CP were recruited to evaluate gait training with tSCS and a resistive exoskeleton (Table 6.1). Prior to enrollment, informed age-appropriate assent and consent were obtained from participants and their caregivers. All visits were completed at the University of Washington, and this study was approved by the University of Washington Human Subjects Division (IRB identifier: STUDY00014877) and registered at ClinicalTrials.gov (NCT05520359). Individuals

were eligible to participate if they were ambulatory children with spastic CP, Gross Motor Function Classification System (GMFCS) Levels I-II who did not have a history of selective dorsal rhizotomy, had not undergone a lower extremity surgery or botulinum toxin injections in the past year, did not have uncontrolled seizures, were able to follow 2-3 step commands, and had no other conditions that might make participation unsafe, decided at the discretion of the research team.

Table 6.1 Participant Characteristics

ID	Sex	Age (years)	Height (cm)	Weight (kg)	Diagnosis	Side	GMFCS Level	Speed (m/s)	tSCS Amplitude (mA)	
									T11	L1
P01	M	14	169	64.3	Uni-spastic	R	I	1.2	30	20
P02	M	4	109	17.2	Bi-spastic	L	I-II	0.82	35	25
P03	M	13	155	38.6	Bi-spastic	R	II	1.0	20	30
P04	M	15	160	48.2	Bi-spastic	L	II	0.9	35	25
P05	F	6	117	20.5	Bi-spastic	R	II	0.6	10	20
P06	F	6	113	19.5	Bi-spastic	R	II	0.65	10	15-20
P07	F	13	157	51.3	Bi-spastic	L	I	1.0	20	30
P08	M	15	163	58.3	Bi-spastic	L	II	1.05	30	20
P09	M	11	135	39.0	Uni-spastic	R	II	0.8	10	20

ID = participant identifier; Bi-spastic = bilateral spastic CP; Uni-spastic = unilateral spastic CP; Side = more affected side based on the side with more spasticity at baseline and parent reports; GMFCS = Gross Motor Function Classification System Level; The tSCS amplitude applied to T11 = thoracic spinous process 11, L1 = lumbar spinous process.

6.3.2 Experimental Protocol

Participants attended four visits where they walked for up to 20 minutes with or without our devices with rest breaks provided as needed. These walking tasks included: no devices (walking), tSCS only (tSCS), resistive exoskeleton (Exo), or the combination of tSCS and Exo (tSCS + Exo). P06 and P07 did not complete the tSCS+Exo visit due to circumstances unrelated to the study. Participants walked on the treadmill at a preferred speed that was determined at the first visit and held consistent at subsequent visits. Walking tasks were performed on a split-belt inground treadmill (Bertec, Columbus, OH) on separate days at least five days apart in a pseudo-randomized order.

For the tSCS and tSCS+Exo visits, tSCS was administered via a non-invasive spinal cord stimulator (SCONE^{TM}, SpineX, Inc.) following previously reported protocols [17]. Stimulation was applied using adhesive gel electrodes placed just below the T11 and L1 spinous processes using 3.2 cm round electrodes. The ground electrodes were 5.1 x 8.6 cm rectangular electrodes placed over the anterior, superior iliac spine (ASIS). The amplitude for the subthreshold stimulation was determined for each individual at their first visit using tSCS and held consistent at subsequent visits (Table 6.1). The amplitude of tSCS was determined based on children's self-report of quality of walking, sensation beneath the cathodes, and a physical therapist's clinical observation of gait quality and participant's behavior withing the first 10-minutes of use. Then tSCS was turned off and a break was provided until the 10-minute walking task began. The amplitude of tSCS was also lowered or turned off if participants took a seated break during the 20-minute walking task. For the Exo and tSCS+Exo walking conditions, the ankle resistance torque of the Exo was set at 12% of each participant's bodyweight, similar to what has been used previously to engage the plantarflexors in children with CP [84].

During all walking tasks, electromyography (EMG) data from the soleus muscle were recorded on the more-affected limb at 2000 Hz (Delsys, Inc., Natick MA) for the first five minutes of walking. Before (pre) and after (post) the walking task, maximum voluntary contraction (MVC) of the more affected plantarflexors were obtained using the manual muscle test with a hand-held dynamometer (Activbody Inc., San Diego, CA). Participants laid supine and were instructed to keep their knees fully extended while plantarflexing their foot as forcefully as possible for 5 seconds against a researcher providing resistance with the hand-held dynamometer [90]. Participants were given visual feedback of the force value reached throughout the 5-seconds and instructed to get the number as high as possible and keep pushing for the duration of the 5 seconds. The MVC was repeated 3 times at each timepoint, and EMG data of the soleus muscle was recorded throughout.

6.3.3 Data Analysis

Soleus median frequency (MDF) and signal amplitude where used as biomarkers for myoelectric manifestations of muscle fatigue [215], [221]. EMG data for walking tasks were analyzed using a custom MATLAB script (MathWorks, Natick MA). Soleus EMG signals were bandpass filtered from 20 – 400 Hz using a 4th order Butterworth filter. Soleus firing rate was quantified by segmenting bandpass filtered soleus EMG using a Gabor transform moving window centered at 15-second intervals and calculating the median frequency [154], [173]. The Gabor transform filters EMG data in the time domain using a Gaussian function,

$$g(t) = e^{-a(t-b)^2}, \tag{1}$$

where $a = -0.01$ is the window width of the filter, t is the time, and $b = 15$ seconds is the distance between centers of the moving window. The MDF was determined using the built-in MATLAB function, medfreq(), to find the median frequency of the time-domain EMG data power spectrum. EMG data were then zero-centered, rectified, and low-pass filtered (4th order Butterworth; 10 Hz) to generate a linear envelope to quantify soleus peak activation. Soleus peak activation was defined as the maximum soleus EMG amplitude of the low-pass filtered EMG signal in 15-second intervals. Soleus firing rate and peak activation were normalized to the calculated firing rate and peak activation of the first 15 seconds of walking, respectively.

During the 5-second MVC task, EMG data were also recorded. The same analysis steps described above for EMG analysis during walking were used, except the interval for the Gabor filter and calculating EMG amplitude were divided into 0.5-sec segments. The average EMG amplitude, MDF, and peak MVC force were used to generate box plots to represent myoelectric manifestations of muscle fatigue during a maximal voluntary task before and after each walking task. P07 did not

complete MVC tasks due to sensory sensitivity. Values are reported as median [range].

6.3.4 Statistical Analysis

We used linear regression to quantify the rate of myoelectric manifestations of muscle fatigue with the EMG amplitude and MDF across the 5 minutes of treadmill walking. The One-sample Kolmogorov-Smirnov test was used to check for normal distributions in the datasets: MVC force, MVC EMG amplitude, MVC EMG MDF, rate of change of EMG amplitude during the first 5-minutes of walking, and rate of change of EMG MDF during the first 5-monutes of walking. Then either one-way ANOVA or the non-parametric Kruskal-Wallis were performed.

6.4 RESULTS

Median changes in MVC force, EMG amplitude, and MDF were less than 20% after completing each task (Figure 6.1). The change in MVC force, EMG amplitude, and MDF were not significantly different between tasks ($p > 0.20$). Median changes in MVC force were -10 [-51-+23] Newtons (N), -3 [-15-+41] N, -1 [-15-+34] N, and -13 [-21-+7] N after walking with no devices, tSCS only, Exo only, and tSCS+Exo, respectively. The force produced during the MVC task increased after Exo training by 6%, and decreased after training with no device, tSCS only, and tSCS+Exo by 18%, 3% and 9%, respectively. EMG amplitudes during MVC decreased 3% after training with Exo and no device but increased by 5% and 9% after training with tSCS and tSCS+Exo, respectively. The EMG MDF during MVC increased 7%, 5%, 3%, and 8% after training with no device, Exo, tSCS, and tSCS+Exo, respectively.

Participants fatigued during all four walking tasks, but the rate of fatigue was greatest during Exo training (Figure 6.2). Training with no devices and tSCS only produced a small increase in EMG amplitude (+12% and +5%, respectively) with negligible changes in MDF (+2% and -5%, respectively). During Exo training, EMG amplitude increased 83% at a rate of 13% per minute, while MDF decreased 19% at a rate of 5% per minute. During training with tSCS+Exo, the EMG amplitude increased 22% at a rate of 5% per minute; however, the MDF also increased 4%. The rate of change of EMG amplitude and MDF were not significantly different between tasks ($p > 0.06$) (Figure 6.3).

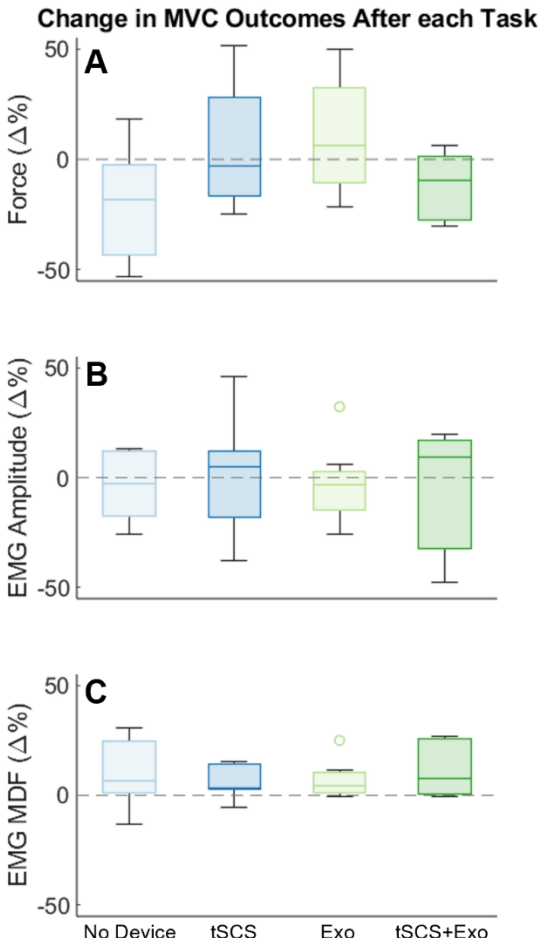
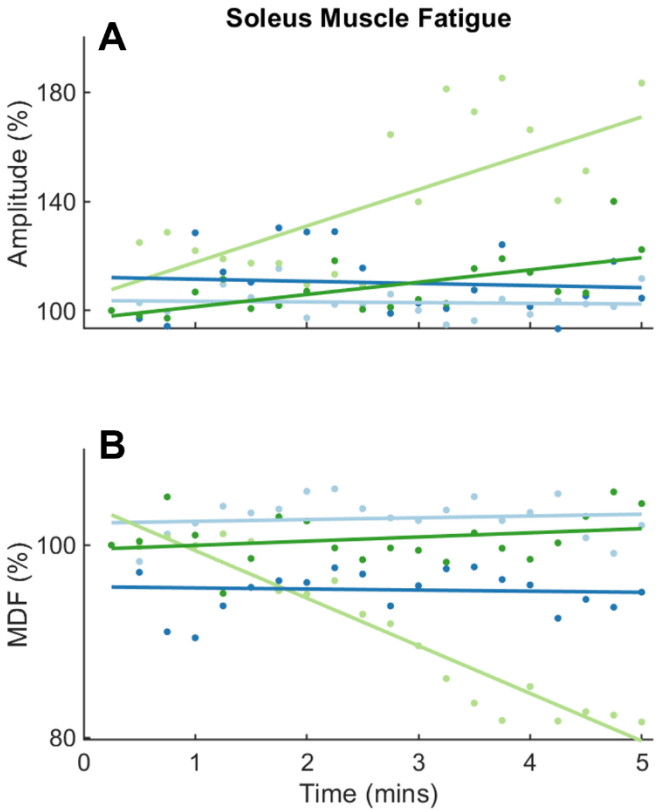


Figure 6.1 Percent change in maximum voluntary contraction (MVC) A) peak force, B) electromyography (EMG) peak amplitude, and EMG median frequency (MDF) after each walking task: walking with no devices (No Device), walking with spinal stimulation (tSCS), walking with a resistive exoskeleton (Exo), and walking with both tSCS and Exo (tSCS+Exo).

6.5 Discussion

As hypothesized, training with a resistive ankle exoskeleton induced the greatest rate of muscle fatigue within the first five minutes of walking, with a simultaneous increase in EMG amplitude and decrease in MDF. The same rate of fatigue was not present during the tSCS+Exo condition, suggesting that tSCS may reduce the impact of the resistive exoskeleton on muscle fatigue during training. Walking with no devices or with tSCS only were very similar in their rates of muscle fatigue, suggesting that five minutes of treadmill training at a comfortable speed

induced minimal myoelectric manifestations of muscle fatigue. Changes in MVC EMG amplitude and MDF were minimal after each task, while MVC force decreased most after walking with no devices.



Amplitude Linear Regression

	R^2	Slope	% Change
No Device	.01	-0.3	+12
tSCS	.01	-0.8	+5
Exo	.51	13.0	+83
tSCS+Exo	.41	4.5	+22

MDF Linear Regression

	R^2	Slope	% Change
No Device	.02	0.1	+2
tSCS	0	-0.1	-5
Exo	.91	-5.0	-19
tSCS+Exo	.06	0.4	+4

Figure 6.2 Myoelectric manifestations of muscle fatigue during five minutes treadmill training under the four different conditions: no device, tSCS only, Exo only, and tSCS+Exo. A) The amplitude of the electromyography signal normalized to the peak amplitude during the first 15 seconds of each task. B) The median frequency (MDF) of the electromyography signal, normalized to the MDF in the first 15 seconds of each task. Information from linear regressions is included, with % Change indicating the percent change in the outcome from the first to last 15-sec increment.

Prior research has suggested that children with CP show similar and even reduced rates of fatigue compared to nondisabled peers during tasks requiring maximal effort, but this maximal effort (i.e. force output) is also reduced [222], [223]. We observed minimal changes in the maximum EMG amplitude or MDF during the MVC task performed before and after each walking task. These findings suggest that the 20-minute walking task did not affect participants'

ability to perform a brief, maximal effort task. Surprisingly, there was a decline in force output after walking with no devices more than other tasks. The increased sensory feedback when using either Exo or tSCS may improve coordination of muscles and increase the ability of the user to maximally engage in the MVC task [21], [91]. This may allow for maintenance in MVC force output after these tasks despite evidence of muscle fatigue during the training compared to no devices, as observed here.

Prior work indicates that children with CP are not able to activate as large a volume of muscle fibers during volitional maximal effort tasks compared to their typically developing peers [224]. As a result, we may observe muscle fatigue more accurately during the walking task, where the demand on muscles is actually higher than during the MVC task. This could relate also to the level of refined motor control within a muscle group. Fifteen minutes of treadmill training has been shown to reduce MVC force in the quadricep muscles by 11% in children with CP, with no change among typically developing peers [225]. Children with CP typically have less refined motor control in their more distal extremities, so relying only on the force from MVC only before and after a task as a measure of plantarflexor fatigue may not be an accurate representation of fatigue with more functional tasks for this population.

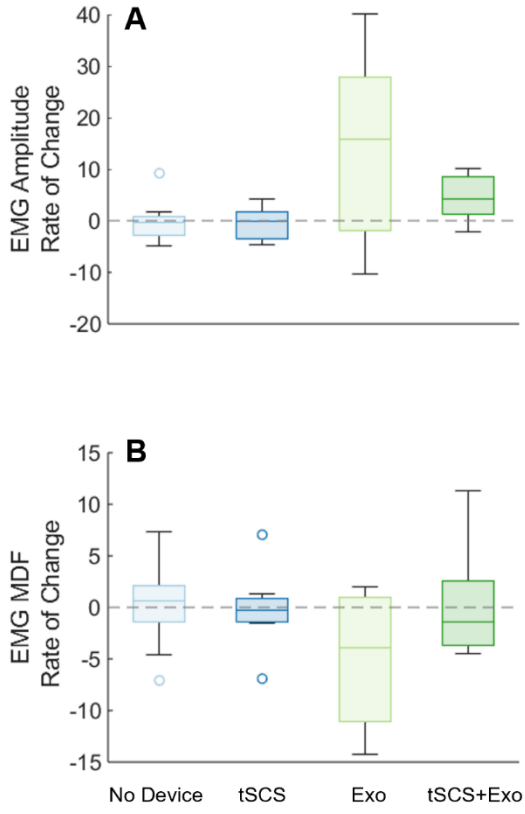


Figure 6.3 Rate of change of A) EMG Amplitude and B) EMG MDF during the first 5-minutes of walking. Groups were not statistically significantly different (Amplitude: p = 0.6; MDF = 0.49).

Children with CP who walk with crouch gait have greater muscle fatigue during 5-minutes of walking compared to typically developing peers. Eken et al., 2019 reported a significantly greater rate of fatigue via increases in EMG amplitude in the gastrocnemius and soleus muscles on the more-affected side of children with CP and non-significantly greater rates of muscle fatigue as quantified via EMG MDF in the same muscles [173]. This study evaluated overground walking, while walking on a treadmill may offload the plantarflexors and put more demand on the quadriceps. Parent et al., 2019 reported significant reductions in rectus femoris MDF across six minutes of treadmill walking in children with CP who walk with crouch gait, but no change in other muscles [154]. We, similarly, did not observe myoelectrical manifestations of fatigue in the soleus muscle during treadmill walking, but walking with the resistive Exo did increase rate of fatigue as evidenced by changes both in MDF and amplitude. The variability was high across participants with the Exo, likely a cause of the different rates of change within the first five minutes not being statistically significantly different (Figure 6.3).The exoskeleton provides a dorsiflexion torque that counters the desired action at push-off, to encourage the user to increase plantarflexor engagement [90]. The increased rate of fatigue during training with the Exo suggests that the Exo successfully engaged the soleus more and drove up the rate of fatigue in this muscle.

We observed an increase in EMG amplitude and minimal change in MDF during the five minutes of walking with tSCS+Exo (Figure 6.1). A simultaneous increase in EMG amplitude and MDF suggests that participants were increasing their force output during the task and not yet showing signs of fatigue in the muscle [221]. These findings suggest that tSCS enabled more engagement with the resistive exoskeleton to generate a greater force at the ankle, as shown by

increased EMG amplitude, while walking with minimal effect on fatigue, as shown by no change in MDF.

We only included the first five minutes of walking in our regression analysis, similar to prior studies on fatigue during walking in children with CP [154], [173]. Given minimal changes in muscle fatigue have been observed during treadmill walking for children with CP within the first five minutes, a longer duration may be needed. This presents a challenge given that rates of fatigue are expected to become more nonlinear while longer periods of assessment [226]. Future work could address this gap by seeking nonlinear modeling techniques to quantify these relationships. We also only quantified fatigue in the soleus muscle, as the exoskeleton primarily targets plantarflexion and blocks the gastrocnemius from being recorded. This task may also increase engagement of other muscles, such as the rectus femoris. Thus, other lower extremity muscles should be considered in future work. Finally, MVC was quantified with a manual dynamometer with resistance to plantar flexion provided by a researcher. Measuring MVC with a manual dynamometer is a common practice [90], [222], [227], [228], but use of a isokinetic dynamometer would produce more accurate measurements.

Walking with a resistive ankle exoskeleton increased the rate of muscle fatigue during five minutes of treadmill walking compared to walking with no devices. The addition of tSCS reduced fatigue in the soleus muscle and likely increased force output and thus engagement with the device. These results suggest that tSCS may be a viable tool for reducing muscle fatigue during training to maximum rehabilitation benefits of physical therapy for children with CP.

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6.7 Conflict of Interest Statement

Chet T. Moritz serves as a clinical advisor to the company SpineX, who provided the stimulator for the study. SpineX also licensed IP generated by the team at the University of Washington, Chet T. Moritz, Katherine M. Steele, Siddhi R. Shrivastav, and Charlotte D. Caskey.

Chapter 7

CONCLUSION

7.1 SUMMARY

The goal of this dissertation was to leverage tools in mechanical engineering and neuromechanics to quantify responses to neuromodulation and physical therapy in children with CP. This dissertation presents some of the first work to quantify the effects of non-invasive neuromodulation on walking function in children with CP. Specifically, it is the first to examine changes in clinical assessments of walking function alongside changes in the neuromechanics of gait when tSCS is used with treadmill training. Additionally, this dissertation is the first work to use causal modeling and machine learning to quantify individual responses to rehabilitation while controlling for changes in movement and the rehabilitation program, which often can make it challenging to isolate and understand outcomes. Finally, this dissertation encompasses the first study to combine tSCS with a resistive exoskeleton as a method to interrogate the mechanisms behind tSCS and its effect on neuromuscular control. Overall, this work provides insight into how tSCS affects walking for children with CP and provides methods for understanding individual rehabilitation progression.

A key objective of this dissertation was to quantify the effect of tSCS applied during treadmill training on spasticity, walking function, and neuromechanics of gait in children with CP. In Chapter 3, we quantified these outcomes in four children with spastic CP in a single-arm pilot study. This work provided a detailed examination of how tSCS affects body structure, function, and activities of daily living. We found that reductions in spasticity were nearly three times greater when tSCS was applied during 24-sessions of gait training compared to the same gait training without tSCS. Such large reductions in spasticity from other forms of treatment can often come

with a decline in walking function, but our participants maintained walking function both in the lab and the community. In Chapter 4, we narrowed in on individual participants' changes in gait neuromechanics, finding that all participants reached the greatest extension at the hip and knee after tSCS+SBLTT. This suggests that they are in a more upright, less fatiguing posture after training with tSCS. This work was a pilot study with a small sample size, but the findings have been exceptional in motivating future work across a larger sample size to understand if the findings will continue to support the use of tSCS for children with CP.

In rehabilitation, clinicians are required to make decisions within and between sessions on how to adapt a therapy program to an individual. This was true in our interventions and is a near-universal challenge of rehabilitation programs. Clinical expertise is critical in this decision-making process, but it can still be challenging to subjectively assess progress when many factors can influence how or if someone may be benefiting from an intervention. Many factors, such as a child's age, day-to-day fatigue, level of challenge, or lab distractions, are often highly variable, interconnected, and non-linear. In Chapter 5, we validated and applied a causal model and machine learning paradigm to track step length progression during treadmill training. With an *in silico* dataset, we validated the high accuracy of this paradigm in capturing progression in step length with training despite nonlinearities in progression and high variability in the data set. We then applied it to a sample dataset with four children with CP to provide examples of how progression within training, such as speeds, can mask changes in step length with session progression. This paradigm can be applied to other rehabilitation programs where data can be collected during sessions and be used to track progress and provide more information for an interventionist about optimal treatment for an individual.

With novel interventions such as neuromodulation or exoskeletons, a better understanding of how users respond to devices within a training session can also be informative for individualizing treatment. One aspect of developing our understanding of novel devices is tracking fatigue and muscle engagement during rehabilitation sessions to find the balance between providing challenging tasks that optimized motor learning without leading to overexertion. In Chapter 6, we quantify how tSCS and a resistive ankle exoskeleton (Exo) affect muscle fatigue during and after a single training session. We found that walking in the Exo only condition led to the greatest rate of fatigue compared to walking with no devices, tSCS only, and tSCS+Exo. These findings suggest that tSCS may be able to delay the onset of muscle fatigue during training and increase muscle engagement, especially during more demanding tasks, such as walking with a resistive exoskeleton.

7.2 Future Work

The work outlined in this dissertation lays the foundation for continued research translating novel interventions into clinical care by first understanding their effect on body function and structure, as well as how to accurately track drivers of therapy progression. The results of these studies suggest impactful future research to continue to bridge the gap between our research and the translation to clinical care. The following sections outline potential avenues for future research based on the findings discussed in this dissertation:

7.2.1 Quantify Individual Responses to Neuromodulation and Haptic or Audiovisual Feedback

Chapter 5 developed and validated Bayesian Additive Regression Trees (BART) for tracking individual responses to treadmill training. This method could be applied to other rehabilitation interventions, such as optimizing exoskeleton or neuromodulation parameters for rehabilitation that were discussed in other dissertation chapters. These novel technologies have a variety of

parameters that can be adjusted on an individual basis, such as the applied torque for the resistive ankle exoskeleton and the amplitude of tSCS. Both of these parameters have been shown to optimize differently across individuals and are important considerations when delivering physical therapy [17], [90], [91], [114], [115]. Current implementation of these devices relies on initial assessments and/or the observation of a clinician. Use of BART to quantify individual changes in movement in response to treatment decisions during therapy could be helpful in isolating the direct effect of each parameter on the outcomes while controlling for other changes. Tracking each parameter's effect on outcomes would support clinical decision-making. BART may also be used to understand how changes to parameters, like exoskeleton torque and stimulation amplitude, affect movement patterns.

7.2.2 Quantify the Underlying Neurophysiological Changes in the Central Nervous System with Neuromodulation

Chapters 3, 4, and 6 showed how transcutaneous spinal cord stimulation (tSCS) affects the neuromechanics of gait in children with CP. This work informed our understanding of how tSCS affects movement and leads to improved or maintained clinical outcomes. However, we do not fully understand the neurological changes induced by tSCS. Early magnetic resonance imaging (MRI) studies have shown that repeated use of tSCS may increase cortical activation [111], as has been hypothesized in CP [21]. We have also seen reductions in spasticity with tSCS that were not present in training interventions without tSCS (Chapter 3). Increases in cortical excitability, leading to increased presynaptic inhibition in the muscles, could be a driver of reduced spasticity [229], [230]. Studies with unimpaired adults have shown that tSCS can reduce the Hoffman reflex, or H-reflex, the electrical equivalent of the stretch reflex [231]. The stretch reflex is a natural reflex that contracts our muscles when they are elongated to prevent overlengthening of the muscles and

damage to muscle fibers. This reflex is hyperactive in people with spasticity and thought to be an underlying cause of spasticity. The combination of structural imaging of the central nervous system, such as with MRI, and neurophysiological tests, such as H-reflex, can help us understand if changes to pathway excitability cause reduced spasticity with tSCS in children with CP.

7.2.3 Optimizing Rehabilitation from a Fatigue Perspective

We observed in Chapter 6 that the rate of muscle fatigue is impacted by the devices used during the walking task. Ours and prior work is limited by only examining fatigue during walking in a 5-6 minute period [154], [173], when most physical therapy sessions where these devices might be used for 30-60 minutes. Using an animal model, a fatigue-controlled training session that provided frequent rest breaks at the onset of muscle fatigue showed that the session that took breaks to prevent fatigue resulted in greater neuroplasticity [220]. While breaks are provided based on perceived exertion, such as with the OMNI score during SBLTT [232], we still do not understand if these measures align with muscle fatigue or if they are implemented in such a way to optimize the duration and frequency of rest breaks during therapy. Future work should consider more quantitative techniques for assessing muscle fatigue during therapy to further personalize care and optimize opportunities for neuroplasticity and motor learning during training.

7.2.4 Understanding Effective Options for Adults with Cerebral Palsy

CP is often thought to be primarily a pediatric disorder, but with the advancement of medicine, children with CP grow into adults and still require specialized care. Unfortunately, the research on supporting mobility for adults with CP is limited, even though we know function declines with age [5], [233]. The younger brain is more adaptable to learning new skills and generally thought to be more responsive to treatment, also motivating the breadth of research on children with CP. However, this does not mean that adults with CP would also not respond to an

intervention, although it might occur at a different rate or require different protocol designs to maximize efficacy. Incorporating these methods and devices into clinical care for adults with CP, with additional assessments on how neurophysiology changes to help understand if age is a factor in intervention responsiveness, represents an exciting area for future work.

7.2.5 Qualitative Assessment of User Interest in Novel Devices

When considering implementation of these techniques into clinical care, it is also important to understand participant and family perception of these devices. Historically, people with disabilities have reported some negative experiences with pediatric rehabilitation, such as the outcome goals set by a therapist not aligning with their personal goals [234]–[236]. With the end goal to support people seeking pediatric rehabilitation, it is critical these voices are heard and included early in the research process. Understanding child, parent, and caregiver interpretation and expectations with novel devices is valuable for ensuring researcher goals align with the goals of the users and to start addressing any barriers to implementation early on. Qualitative interviews and surveys with participants and their parents/caregivers represent methods to capture user perceptions and expectations Participants can inform researchers how a device feels, while parents and caregivers can provide information on changes that they observe in child function when using a device that researchers may not be able to quantify directly. We can also inquire about their interest in using a device in the future, challenges they foresee in implementation, and what needs they would like to address with these devices. Including both qualitative and quantitative assessments in harmony can inform translation of research to the community.

7.3 IMPACT

The long-term goal of the work presented in this dissertation is to support evidence-based practice in clinical care that is focused on optimizing rehabilitation for the individual person. These

findings lay the foundation for understanding how novel techniques may benefit children with CP and through what mechanisms these goals may be achieved. Through the combination of mechanical engineering, neuroscience, and rehabilitation science we comprehensively evaluate human movement and how to quantify changes in mobility with rehabilitation. Future work can build on this preliminary evidence to continue to translate investigational devices into clinical practice.

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