Spinal Neuromodulation and Gait Training for Children with Cerebral Palsy: From Laboratory to Community

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Abstract

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Cerebral Palsy (CP) is a movement disorder that is caused due to an injury to the developing brain around the time of birth. CP leads to abnormal posture, muscle tone and movement, that negatively affects physical function. Children with CP are less active than typically developing children. They experience participation restrictions due to impaired mobility. Currently, there are no non-invasive medical or surgical treatments that can improve children's muscle tone along with mobility. Moreover, the effects of current physical therapy, medical and surgical interventions on children's community walking, participation and quality of life is less known.

Non-invasive neuromodulation, such as transcutaneous spinal cord stimulation (tSCS) may improve children's muscle tone, walking function and mobility. tSCS, when combined with appropriate task-specific exercises, can harness neuroplasticity and thereby lead to long-term improvement in function. There is growing evidence of functional recovery in people with spinal

cord injuries. tSCS may normalize the brain-spinal cord connectivity in CP, thereby leading to positive changes in movement and function. These functional gains may translate into children's community walking, participation and on quality of life.

First, we review background on CP and discuss about impairments associated with CP. We then present on current medical and surgical standard of care for muscle tone management, and discuss physical therapy and rehabilitation practices to improve function in children with CP. We also summarize evidence on high-intensity treadmill training, the short burst interval treadmill training or SBLTT to improve walking function in children with CP. We discuss the potential mechanisms of tSCS in CP and summarize previous evidence of this technique for CP rehabilitation. We provide evidence on the effects of tSCS combined with SBLTT on improving muscle tone, while simultaneously improving lab-based walking function in two children with CP. We then demonstrate the long-term effects of the combination of tSCS and SBLTT on muscle tone, walking function, along with a pre- post-treatment comparison of self-reported walking and health-related outcomes. Lastly, we explore the use of StepWatch device to measure community walking performance after two interventions, SBLTT only and tSCS combined with SBLTT in children with CP. Specifically, we evaluate six variables of walking performance: (1) average strides per day, (2) percent time and (3) number of strides intensities at low, moderate, and high stride rates, (4) percentage of total strides at low, medium, and high intensities, (5) average peak stride rate, and (6) activity index.

This research was conducted with the approval of Human Subjects Division (HSD)

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Plain Language Summary

Cerebral Palsy is a condition that affects muscle control and movement. It is caused by damage to the developing brain, before, during or after birth. Difficult with walking is a common effect of cerebral palsy. This occurs because the connection between brain and the muscles is hampered, and the nerves that control muscles may not work optimally. This leads to increased tone in muscles, which negatively affects children's mobility, participation and quality of life.

Current muscle tone management techniques include medications such as baclofen, botulinum toxin injections and a surgery called the selective dorsal rhizotomy. These techniques are either invasive, permanent, or have side effects that can be unfavorable to children's development. They also negatively affect children's walking function. Therefore, there is a critical need to study new methods that can improve muscle tone, while also facilitating children's mobility, participation and quality of life.

Transcutaneous spinal cord stimulation is a form of electrical stimulation that has shown promise to improve function in people with spinal cord injuries and children with cerebral palsy. This electrical stimulation can be delivered on the surface of skin through electrodes.

Physical therapy interventions often utilize treadmill training to improve walking function and mobility. Treadmill training provides high repetitions of steps in a relatively safe manner. Traditional treadmill programs, however, are based on adult walking patterns and may not be most effective for children. Short burst interval locomotor treadmill training is a high-intensity treadmill training based on children's walking patterns. It improves children's walking endurance, speed and walking in the community.

In this research, we investigated whether the effects of transcutaneous spinal cord stimulation combined with short burst interval treadmill training had more effects on muscle tone, walking function, mobility and community walking, as compared to short burst interval treadmill training alone. A total of four participants were included in this study. We compared the effects resulting from short burst interval treadmill training alone to that of the combination of spinal stimulation and short burst interval treadmill training.

Our findings showed that the combination of spinal stimulation and short burst interval treadmill training led to considerably greater improvements in muscle tone, along with simultaneous improvements in walking function. These improvements were sustained for 3-months without any additional treatment. Additionally, children and their parents reported higher walking scores after the combination of spinal stimulation and short burst interval treadmill training, as measured through self-reported questionnaires. Both interventions led to more intense walking in the community in daily life. Taken together, these results show that the combination of transcutaneous spinal cord stimulation and short burst interval treadmill training leads long-term to improvement in function in children with spastic cerebral palsy.

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Chapter 1. Introduction

This thesis explores the effects of short burst interval locomotor treadmill training (SBLTT) and transcutaneous spinal cord stimulation (tSCS) on spasticity, walking function and community walking in children with spastic cerebral palsy. SBLTT is a specialized form of treadmill training that is based on children's walking patterns. tSCS has the potential to neuromodulate the spinal circuitry and has been most thoroughly studied in people with spinal cord injuries. This dissertation utilizes our understanding of the mechanisms of tSCS from spinal cord injury research and, for the first time, evaluates its application along with structured task practice in the form of treadmill training, in children with CP. In this chapter, I will provide an overview of cerebral palsy pathophysiology, current standard of care and spasticity management approaches, evidence of spinal cord stimulation, and short burst interval locomotor treadmill training.

1.1 Cerebral Palsy

Brain development during childhood is an integral component of our long-term functioning and wellbeing. Injury to the developing brain can cause a child to experience lifelong physical and/or mental disabilities. Cerebral Palsy (CP) is an umbrella term for a group of disorders of movement and posture, caused by a non-progressive interference in the developing brain before, during or within the first two years after birth. CP is the most common cause of motor disability in childhood, with a prevalence of 2-3 per 1000 births (Maenner et al., 2016). About 1 in 345 8-year-old children in the United States are diagnosed with CP (Durkin et al., 2016). Risk factors of CP include low birth weight, pre-term birth, infections and birth complications during pregnancy, and medical conditions of the mother (MacLennan et al., 2015; van Naarden Braun et al., 2016). CP is often characterized by muscle weakness, impaired coordination of muscles and spasticity characterized by hypertonia, hyperreflexia, clonus, spasms and co-contraction (Poon & Hui-Chan, 2009).

1.1.1 Spinal Cord Pathophysiology in CP

The deep periventricular white matter is metabolically susceptible to injury in preterm infants (Back, 2017; Back et al., 2005). Injury to the periventricular white matter, which is a common occurrence in children with spastic CP, leads to diminished inhibitory input to the spinal interneurons from descending neural pathways (Ghai et al., 2013). This causes excessive alpha motor neuron firing in the spinal cord, thereby manifesting as spasticity in the muscles (Trompetto et al., 2014)

The maturation of spinal locomotor circuits is impaired in children with CP. In typically developing people, walking involves lower limb muscle activation, which requires coordination of multiple neural networks that are interconnected. This coordination is diminished in CP due to inappropriate control of supraspinal signals at the level of spinal cord (Cappellini et al., 2016). It has also been suggested that the interlimb locomotor coordination that is required for walking, may depend mostly on the coupling between spinal pattern generators, coordinated by brainstem mechanisms, rather than primarily on cortical structures in CP (Meyns et al., 2014).

Motor problems in CP are associated with damage to the motor pathways from the brain (Cappellini et al., 2020; Cavarsan et al., 2019). The supraspinal-spinal connections are functionally aberrant in CP (Edgerton et al., 2021). It is hypothesized that these abnormal connections can be transformed into functionally normal connections by maximizing the dominance of proprioception and spinal networks that convey sensory input to the brain. That is, the disrupted spinal networks can be transformed into a more normal physiological state through neuromodulation and activity-dependent exercises. This could lead to near-normal proprioceptive ensembles that would project to spinal networks. Additionally, proprioceptive input has the potential to override disruptive descending input and reorganize connectivity for more coordinated movements. There is evidence that more normal ascending sensory inputs can help to form more normal networks that produce descending motor networks (Edgerton et al., 2021).

In summary, the cerebral pathology occurring in CP leads to secondary manifestations in the spinal cord. Specifically, there is atypical development and abnormal maturation of brain-spinal cord connections as children grow. These secondary changes in spinal cord physiology, often influence motor function and walking negatively. Therefore, interventions that target the spinal cord circuits to strengthen the spinal-supraspinal connectivity, may be of value in the field of CP rehabilitation.

1.1.2 Clinical and Topographical Presentation

CP is a heterogenous disorder that encompasses a range of clinical categories and motor impairments. Four main motor types of CP are described in the literature: (1) spastic, (2) dyskinetic, (3) ataxic, and (4) and hypotonic CP (McIntyre et al., 2011). Spastic CP is characterized by hypertonicity and is the most common type of CP. Dyskinetic CP is the second common type and presents with athetosis or dystonia. Ataxic CP primarily presents with difficulties with coordination, whereas hypotonic CP presents with decreased muscle tone and muscular weakness. Currently, CP is not curable, and is managed on a case-to-case basis, depending on symptoms and functional impairments that are present.

Topographically, CP can be described as unilateral or bilateral. In unilateral CP, one (monoplegia) or both (hemiplegia) limbs on the same side may be affected. These include (1) diplegia, meaning that lower limbs are more affected than upper limbs, (2) triplegia, meaning that there is unilateral involvement in the upper limbs and bilateral involvement in lower limbs, and (3) quadriplegia, meaning that all four limbs along with the trunk are affected due to CP (Graham et al., 2016). Of these, hemiplegia and spastic diplegia are the most common sub-types. Hemiplegic CP represents the effects of a perinatal stroke. Spastic diplegia is usually accompanied by periventricular white matter loss.

About 66% of children with CP are ambulatory, with or without use of assistive devices (Durkin et al., 2016). Ambulatory children with CP are less active than their typically developing peers (Bjornson et al., 2007, 2011, 2014). They demonstrate increasing levels of non-walking activity as they age (Bjornson et al., 2007). Locomotor skills deteriorate in about 44% of ambulatory children with CP as they transition into adolescence and adulthood (Jahnsen et al., 2004). These findings highlight the importance of targeting gait interventions in early childhood.

1.1.3 Gross Motor Function Classification System

The Gross Motor Function Classification System, or GMFCS, is a 5-level clinical classification system that describes gross motor function of children with CP. It is built on self-initiated movement, with emphasis on sitting, transfers, and mobility (Rosenbaum et al., 2008). Distinctions between levels are meaningful outcomes from day-to-day life. These range from level I, where the child can walk without limitations, to level V, where the child requires a wheelchair for mobility (Palisano et al., 2007). GMFCS is widely used in clinical practice and research to describe the functional abilities of children with CP and to guide treatment planning and intervention strategies.

The GMFCS classification system has several clinical implications. It provides a common language for clinicians, researchers, and families to communicate about the functional abilities of children with CP. It can guide the selection of appropriate interventions (Oeffinger et al., 2004).

For example, an individual classified as level I, who is able to walk without limitations may benefit from treatments that are focused on improving their gait and balance, while an individual classified as level V, who requires a wheelchair for mobility may benefit from treatments focused on improving upper body strength and mobility. GMFCS can also be used to monitor changes in a child's gross motor function longitudinally(Paulson & Vargus-Adams, 2017), and help clinicians to evaluate the effectiveness of interventions and adjust treatment plans as needed.

1.1.4 Participation, Community Ambulation and Quality of Life

Participation is defined as "an involvement in life situation"(World Health Organization, 2002). Participation is especially important in childhood and adolescence as it may have long-term influences on children's health and wellbeing. This is because development occurs through a dynamic interaction between the child, the environment, and the opportunities available to the child (Imms, 2008). A study evaluating leisure activity preferences of adolescence with CP demonstrated that adolescents with CP have preferences for a variety of activities, especially in the social and active-physical domain (Shikako-Thomas et al., 2015). They also reported that preferences were not associated with actual involvement (Shikako-Thomas et al., 2015). This suggests that there may be preferred means of participation that children and adolescents with CP cannot partake, even though they would be keen to.

Children with CP have difficulties participating in activities across home, school, and the community due to limitations in physical functioning and its interaction with the environment (Calley et al., 2012). Even higher functioning children who are independently mobile, also have significantly lower participation levels as compared to their age-matched peers (Calley et al., 2012), which could be because of systemic barriers. These participation restrictions may have a negative effect on their quality of life. A quantitative study found that quality of life was significantly associated with walking performance and physical activity (Mann et al., 2016). Consistently, self-reports from caregivers and children with CP also reveal that quality of life of for children with CP is associated with functioning, physical health and participation (Shelly et al., 2008). Literature also suggests that participation in life is significantly mediated by what children can do motorically in day-to-day life (Bjornson et al., 2013). Collectively, this highlights the importance of rehabilitation interventions that focus on improving walking function and mobility and are translatable to participation-related domains in a child's life.

1.1 Standard of Care

The standard of care for children with CP varies and depends on an individual's specific needs and the severity of their impairments. Usually, a multidisciplinary team approach involving healthcare professionals such as pediatricians, rehabilitation physicians, neurologists, physical therapists, occupational therapists, speech and language therapists, and social workers can be beneficial in providing comprehensive treatment. It is important to note that the management of CP is individualized based on child and their family's goals. Treatment plans are often developed in close collaboration with the child's interdisciplinary healthcare team and family.

1.1.3 Current Spasticity Management Approaches

Spasticity is a velocity dependent abnormal increase in muscle tone that affects about 75% children with CP (Ronan & Gold, 2007). This causes inappropriate, and often excessive muscle activation, which can negatively affect muscle function. Muscle tone regulation is important to maintain normal posture and the facilitate optimal movement.

While spasticity can have multiple origins, in CP it is primarily caused by hyperactivity of alpha motor neurons in the spinal cord due to a loss of typical regulation of motor pathways from the brain (Mukherjee & Chakravarty, 2010). It is important to treat spasticity because if untreated, spasticity may cause muscle spasms, lesser mobility, may impede optimal posture, and reduce quality of life for children (Ward, 2003). Medical and surgical management of spasticity is considered standard of care in ambulatory and non-ambulatory children with CP. Some of the common treatment approaches are discussed below.

1.3.1 Oral and Intrathecal Baclofen

Baclofen is a gamma-aminobutyric acid agonist. This inhibitory neurotransmitter in-turn reduces the downstream release of excitatory neurotransmitters in the spinal cord that contribute to spasticity. It primarily acts at the spinal cord, which makes it a suitable medication for spasticity of both cerebral and spinal cord origins. It can be administered orally or via a programmable intrathecal pump. Because oral medications have the advantage of easy use, they are more frequently used as the first line of treatment for generalized spasticity (Egdar, 2003). Baclofen started gaining popularity after 1977, when a double-blind crossover trial showed that baclofen was significantly more effective than placebo in reducing spasticity and improving passive range of motion (Milla P J & Jackson A D M, 1977). However, recent studies point towards a different outcome. A recent systematic review evaluated six randomized controlled trials involving a total of 130 children with CP. The authors that conducted the systematic review reported that the methodological quality of the original studies was low as they were at a serious risk of bias, there was inconsistency of results, sample sizes were unpowered and clouded by a possible publication bias (Navarrete-Opazo et al., 2016). The systematic review authors also reported that there is conflicting evidence on the effectiveness of oral baclofen in reducing muscle tone, improving motor function or level of activity. In addition, they stated that, while oral baclofen may improve spasticity in non-ambulatory children with excessive spasticity, there is no clear evidence that it is effective in treating spasticity and simultaneously improving function in ambulatory children with CP (Navarrete-Opazo et al., 2016).

Oral baclofen has restricted power to cross the blood brain barrier, and hence it takes higher doses of oral baclofen to seek benefits on spasticity. This is a challenge, especially in children, because baclofen has side effects such as nausea, headache, dizziness, and weakness, which can interfere with children's day-to-day functioning. Intrathecal baclofen (ITB) administration involves surgical placement of a catheter through a small opening in the lumbar dura, with subsequent catheter connection to an implanted baclofen pump, usually placed in the sub-cutaneous tissue of the abdomen (Davidson et al., 2020). ITB can deliver baclofen near the target receptors in the spinal cord, which allows for lower dosage to produce the same reductions in spasticity as using oral baclofen (Brennan & Whittle, 2008). ITB reduces spasticity and improves range of motion but does not improve motor and gait function in ambulatory children with CP (Pruszczynski et al., 2018). A recent systematic review that evaluated research from three decades found that there was no direct link between ITB and improvement in function in children with CP (Buizer et al., 2019). Therefore, the existing evidence on ITB does not show improved walking status, and thereby does not support the clinical use of ITB in ambulatory children with CP.

1.3.2 Selective Dorsal Rhizotomy

Selective dorsal rhizotomy (SDR) is a well-established surgical procedure that permanently transects a subset of sensory nerve roots as they enter the spinal cord to interrupt the reflex circuits that contribute to spasticity. The key objective of SDR is to reduce spasticity in the lower extremities in children with spastic CP. There is consistent and reliable evidence that SDR leads to reduce spasticity in a predictable manner and to a substantial degree in ambulatory children with CP (Wang et al., 2018). However, recent evidence suggests that it does not have an additional benefit over routine therapy for improving walking function in children with CP (Tedroff et al., 2020). Specifically, there are no meaningful differences in walking speed, energy consumption and gait function between people who have an SDR and people who do not participate in the procedure (MacWilliams et al., 2022). Further, there is also no strong evidence that loss of spasticity translates into children's long-term functioning or prevention of contractures (Tedroff et al., 2011). In addition, it has been suggested that people who undergo an SDR, often undergo more subsequent antispastic injections and orthopedic surgeries than children who do not undergo an SDR (MacWilliams et al., 2022). So, even though SDR achieves its primary technical goal of spasticity reduction, it does not have positive effects on long-term walking function, mobility and overall health status of children with CP.

1.3.3 Botulinum Toxin

Botulinum toxin (BTX-A) has been used for several years in the management of spasticity in children with cerebral palsy. BTX-A is a neurotoxic protein that blocks the release of acetylcholine, a neurotransmitter responsible for muscle contraction. By inhibiting the release of acetylcholine, BTX-A causes temporary muscle paralysis, which can be useful for treating muscle spasticity. The toxin is administered through injection into the affected muscle, and the effects last for a few months. BTX-A is particularly used to treat focal spasticity affecting a specific group of muscles (Choi et al., 2016). Injection of BTX-A into the affected muscle reduces muscle tone, improves range of motion, and reduces pain and discomfort (Cioni et al., 2006). Studies have demonstrated the effectiveness of BTX-A in managing spasticity in children with cerebral palsy. For example, a randomized controlled trial found that injection of botulinum toxin significantly reduced muscle tone and improved functional outcomes in children with cerebral palsy (Heinen et al., 2010). Another study reported significant improvements in gait velocity and cadence after BTX-A injections (Wong et al., 2004).

The majority of studies evaluating the effects of BTX-A, however, have focused on a single injection cycle and have used adjunctive interventions (Multani et al., 2019). Therefore, the isolated and long-term effects of BTX-A are less understood. One potential concern is the development of antibody resistance to botulinum toxin, which can reduce the effectiveness of subsequent treatments and require higher doses (Torres et al., 2013). Another potential drawback is the temporary nature of the treatment; botulinum toxin typically lasts for several months, after which the spasticity may return. Additionally, there is some concern that the repeated use of botulinum toxin may lead to partial denervation of injected muscle (Andrew et al., 2000), which may cause long-term muscle weakness.

In summary, current spasticity management options do not take into account the associated muscle weakness or consider the potential long-term effects in the context of the natural history of limited mobility in children with CP. This emphasizes the need for evaluation of newer spasticity management techniques, such as non-invasive spinal cord stimulation, that can also simultaneously improve motor function and mobility in children with CP.

1.2.2 Physical Therapy

Physical Therapy is one of the key services to manage functional impairments and secondary symptoms that are caused by CP. It involves exercises and activities designed to strengthen muscles, improve static and dynamic balance and muscle coordination, and increase flexibility. Physical therapy also incorporates various activities to advance sensory processing and motor planning. Physical therapy interventions usually focus on maintaining and improving motor skills, gross motor function, and minimizing onset of joint contractures (Martin et al., 2010). Some evidence-based physical therapy interventions to improve walking function include environmental enrichment, fitness training, goal-directed training, hippotherapy, home programs, mobility training, strength training, treadmill training, partial body weight support treadmill training, and weight-bearing (Novak et al., 2020). These interventions are frequently based on the modern principles of motor learning and are often prescribed in the form of functional or task-specific training (Magill & Anderson, 2014).

Therapy is often tailored to children’s precise functional needs and may involve both traditional exercises and more specialized activities, such as aquatic therapy or hippotherapy. Specifically, hippotherapy improves spasticity (Lucena-Antón et al., 2018) and posture (Matusiak-Wieczorek et al., 2020), and is celebrated among parents for its positive effects on motor and psychological behavior (Debuse et al., 2009). On the other hand, aquatic therapy has shown consistent improvements in motor functions in children with various levels of motor impairment (Dimitrijević et al., 2012; Lai et al., 2015). The specific treatment approach for motor impairments in CP depends on the individual's unique needs and the specific type and severity of sensorimotor impairments. In general, physical therapy treatment for CP aims to improve motor function, prevent, or reduce secondary complications, and promote participation in activities of daily living.

1.3 Short Burst Interval Locomotor Treadmill Training

Typically developing children and youth demonstrate physical activity patterns that are remarkably different from adult walking patterns. However, anecdotally, all gait and treadmill training programs have been formulated on adult walking patterns. Short burst interval locomotor treadmill training (SBLTT) is a specialized form of treadmill training for children which is based on children’s natural walking patterns (Bjornson et al., 2019). Typically, children engage in very short bursts of intense walking and physical activity interspersed with varying intervals of low and moderate intensity (Bjornson et al., 2014). However, children with CP do not engage in bursts of intensive walking and spend most of their walking activity in low-intensity walking (Bjornson et al., 2007, 2014). SBLTT aims to increase moderate to high intensity strides, while also providing high repetition of steps.

SBLTT involves short, of 30-second bursts of fast walking, interspersed with slower speeds. The primary goal of SBLTT is to increase and maximize the walking speed of the high-speed bursts within and between sessions. The low speed 30-second intervals remain constant throughout the protocol. Treadmill speed is controlled by a research physical therapist. The speed is modified within and between sessions based on individual’s tiredness using children’s OMNI scale of perceived exertion (Fragala-Pinkham et al., 2015), and by clinical observation of skin color, sweat, rate of breathing and the ability to walk and talk. The goal is to train on the SBLTT protocol for 30-minutes. SBLTT can be combined with novel neuromodulation techniques, such as the spinal cord stimulation, with an emphasis to improve walking function.

1.4 Transcutaneous Spinal Cord Stimulation

Transcutaneous spinal cord stimulation (tSCS) is a novel, non-invasive neuromodulation technique that can electrically activate spinal cord circuitry through the skin (Gerasimenko, 2015). It is most commonly applied through 2-3 cm circular adhesive gel electrodes placed on surface of the skin of the cervical, thoracic or lumbosacral vertebrae (Gad et al., 2017; Gerasimenko, et al., 2015; Inanici et al., 2018, 2021; Samejima et al., 2022). tSCS utilizes a stimulation waveform with a carrier frequency of 10KHz, which makes it possible to deliver higher intensities without any pain or discomfort. The unique frequency allows the stimulation to bypass the pain receptors such as C-fibers in the skin. By modulating the spinal cord with this non-invasive stimulation, we can safely use stimulation currents that were previously not possible due to discomfort of the skin.

1.4.1 Mechanism of Action

The neuro-physiological basis of how tSCS improves motor function is not yet completely understood. Some theories suggest that tSCS can modulate the activity of the spinal cord and promote neuroplasticity, leading to improvements in motor function. One of the mechanisms by which tSCS non-invasively modulates the activity of the spinal cord consists of the recruitment of medium to large afferent fibers in the posterior roots (Sayenko et al., 2019). However, it has also been shown that tSCS can engage both afferent and efferent pathways, based on observations of early- and medium-response components of evoked potentials that are partially ascribed to posterior roots, group Ia, group II and motor neurons or anterior roots (Gerasimenko, et al., 2015). Additionally, Gerasimenko also proposed that increasing the stimulation intensity leads to the activation of smaller diameter afferents, and more intraspinal connections and spinal interneurons are recruited. This proposed mechanism brings the interneurons and motor neurons closer to the firing threshold (Gerasimenko, 2015), which can improve supraspinal control in conditions such as CP (Edgerton et al., 2021).

It is important to note that the dorsal root system may not be entirely responsible for the effects of tSCS on motor function. There are other, less understood mechanisms, that may contribute towards functional recovery. Cutaneous mechanoreceptors in the skin may be acting on both sensory and motor processes in the spinal cord. This could alter the excitability where the stimulation is provided as well as remote levels of spinal cord through activation of propriospinal neurons (Barss et al., 2022). Propriospinal neurons are contained entirely within the spinal cord and may have short segmental or multi-segment projections (Cowley et al., 2021). They can transport descending information and participate in the integration of information with afferent sensory feedback from the periphery (Cowley et al., 2008). They also mediate and coordinate rhythmic motor output involving multiple peripheral joints, with corresponding neurons spanning several spinal segments, which makes them an essential element in locomotion (Cowley et al., 2021). Everything considered, it is plausible that the recruitment of cutaneous mechanoreceptors surrounding the electrodes may contribute to the neuromodulatory effects of tSCS through propriospinal connections.

1.4.2 tSCS and Physical Rehabilitation

There has been research on the effects of the combination tSCS and task-specific physical therapy-like interventions in people with spinal cord injury (SCI). A prospective cross-over study with intensive upper extremity functional task training and tSCS revealed that the combination of training and tSCS restored substantial and prolonged upper extremity function in people with both motor complete and incomplete cervical SCI (Inanici et al., 2018, 2021). Similarly, a 4-week intervention program with tSCS and voluntary hand gripping tasks led to improvements in grip strength (Gad et al., 2018). Subjective self-reports from patients uncovered an improvement in performing tasks typically associated with activities of daily living (Gad et al., 2018), which speaks to the translatability of the functional effects of tSCS on people’s daily life. A single-subject crossover study with two individuals with motor incomplete SCI found that the combination of locomotor training and tSCS promoted recovery of locomotor and autonomic functions beyond locomotor training alone (Samejima et al., 2022).

With regards to a CP, literature suggests that accurate proprioceptive feedback is essential to achieve optimal outcomes from tSCS (Edgerton et al., 2021). If paired with the correct activity, it may also have positive effects on motor function in children with CP. A study evaluated the acute effects of single 30-minute session of tSCS in children with CP (Gad et al., 2021). They hypothesized that tSCS combined with movements can facilitate the mechanisms of the spinal cord. This further suggested that these can transform the brain-spinal cord dysfunctional connectivity of CP into highly functional connections, characterized by a more normal agonist–antagonist coordination pattern. tSCS was delivered at T11-12 and L1-2 vertebral levels at an intensity of 20-25% below motor threshold. Functional tasks such as standing and stepping were performed with or without assistance. Children with variable motor function were included. A child who was unable to take steps without tSCS, developed stepping-like patterns when tSCS was applied. Robust alternating EMG bursting activity was observed in all lower extremity muscles after tSCS was applied. Participants who were capable of stepping prior to tSCS demonstrated reduced levels of co-contraction of agonist-antagonist muscles after tSCS. These results indicate that tSCS combined with appropriate proprioceptive training may have the potential to improve motor function in children with CP.

Solopova and colleagues evaluated the effects of tSCS and locomotor training on motor function in children with CP (Solopova et al., 2017). Twenty-eight children with CP and ten typically developing children were randomly assigned to one of the two groups: Experimental group received 12 sessions of Lokomat-based locomotor training with tSCS, and the control group received Lokomat-based training only. In the experimental group, tSCS was initially applied at L1 vertebral level for 5-minutes in an upright posture, and then at T11 vertebral level during the first 10-minutes of locomotor training. They continued with locomotor training without tSCS for the next 20-minutes. They reported increased knee flexion torque and hip range of motion with the combination of tSCS and Lokomat. Muscle co-contraction of agonists and antagonists, which is a major motor challenge in CP (Poon & Hui-Chan, 2009), also reduced in the experimental group. Spasticity did not reduce in either the control or experiential group.

A recent study combined tSCS and activity-based neurorehabilitation. The authors reported that the combination of tSCS and activity-based neurorehabilitation led to gross motor function improvements in sixteen children with CP (Hastings et al., 2022). Activity-based neurorehabilitation was not standardized so as each participant received equal amount and intensity of training. Additionally, there was no control group for comparison. These factors make interpretation of the isolated effects of tSCS difficult. Additionally, lack of comparison group makes it difficult to understand whether the improvements in gross motor function were merely due to the neurorehabilitation therapy. To address these limitations, future research work is required to evaluate the effects of tSCS.

The non-invasive nature of tSCS, along with its specialized waveform makes it a great asset in pediatric neurorehabilitation. Further investigation with tSCS and Physical Therapy interventions, can be useful to determine the clinical utility of tSCS in rehabilitation of children with CP. If demonstrated to have benefits, it can be a very valuable tool in a physical therapist’s toolbox to magnify the effects of physical therapy interventions in children with CP.

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Chapter 2. Transcutaneous Spinal Cord Stimulation and Short Burst Interval Locomotor Training Improve Spasticity and Walking Function in Children with Cerebral Palsy – A Case Series

This chapter is submitted for publication.

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2.1 Abstract

2.1.1 Purpose: To evaluate the effects of combined transcutaneous spinal cord stimulation and short-burst interval locomotor treadmill training (SBLTT) on spasticity and walking function in children with cerebral palsy (CP).

2.1.2 Methods: We conducted a case study with a crossover design in two children (4- and 12-years-old, male) with spastic CP. They completed 24-sessions each of two interventions: SBLTT only and SBLTT combined with spinal stimulation. There was a washout between the intervention phases to account for carry-over effects, and a 3-month follow-up after the second intervention. SBLTT intensity and progression were identical in both interventions and were individualized for each child.

2.1.3 Results: Stimulation combined with SBLTT considerably reduced lower-extremity muscle spasticity. Both participants experienced a 60-70% (12-point) reduction in spasticity when stimulation was combined with SBLTT. This was greater than SBLTT alone (5 points), and improvements persisted over 3 months follow-up. Walking distance, speed, and functional mobility scores improved similarly due to both interventions for both participants.

2.1.4 Conclusions: Transcutaneous spinal cord stimulation appears to be an effective spasticity management tool in children with CP. When combined with SBLTT, it led to the greatest improvements in spasticity with continued improvements in walking endurance, speed, and mobility in two children with cerebral palsy.

2.2 Introduction

Cerebral Palsy (CP) is a non-progressive disorder of movement and posture caused by damage to the developing brain. Eighty-five percent of children with CP present with spasticity (McIntyre et al., 2018), which is characterized by a velocity-dependent increase of muscle tension. Spasticity is a major contributor to functional limitation in children with CP, limiting gross motor function and functional outcomes such as walking (Kim & Park, 2011).

Both temporary and permanent spasticity treatments are considered standard of care for the management of spasticity. Common spasticity treatments for children with CP include botulinum toxin type-A (BTA) injections, baclofen, and selective dorsal rhizotomy (SDR). BTA injections are applied intramuscularly and reduce spasticity by blocking acetylcholine release from motor neurons at the neuromuscular junction (Alexander et al., 2018; Multani et al., 2019). BTA reduces muscle activity for 3-6 months, but improvements in walking function are minimal and short lived (Alexander et al., 2018; Multani et al., 2019). Further, recent evidence has suggested potential long-term negative effects on muscle size and development (Alexander et al., 2018).

Baclofen is a gamma-aminobutyric acid (GABA) agonist that in-turn reduces the release of excitatory neurotransmitters in the spinal cord that contribute to spasticity. Baclofen can be administered orally or via a programmable intrathecal baclofen pump (ITB). While oral baclofen may improve spasticity in non-ambulatory children with excessive spasticity, there is no clear evidence that it is effective in treating spasticity and simultaneously improving function in ambulatory children with CP (Navarrete-Opazo et al., 2016). Similarly, existing evidence on ITB does not show improved walking status, and thereby does not support the clinical use of ITB in ambulatory children with CP(Pin et al., 2011). Phenol is another medical spasticity management option for children with CP. The effects of Phenol are short-lived, however, and the injection is often painful leading to a poor follow-up (Gonnade et al., 2017).

Selective dorsal rhizotomy (SDR) is an invasive neurosurgical procedure that severs afferent nerves in the spinal cord. While this surgery reduces spasticity, long-term functional, participation, and quality of life outcomes of children who have undergone SDR are not significantly different from children who have not undergone the surgery (MacWilliams et al., 2022; Munger et al., 2017).

In addition to spasticity, children with CP have limited mobility and are significantly less active than their nondisabled peers (Baer et al., 2019; K. F. Bjornson et al., 2007). Gait training in the form of weight-bearing treadmill training is most effective in improving walking speed (Moreau et al., 2016), a valid measure of walking activity (Pirpiris et al., 2003, 2006).

In general, children naturally engage in short bursts of low and high intensity while walking (Armstrong et al., 1990; K. Bjornson et al., 2010). Short burst interval locomotor treadmill training (SBLTT) is an emerging training program which is designed to replicate children’s natural activity patterns. It is task-specific training that provides mass practice of stepping on the treadmill. SBLTT has demonstrated improved walking function and community walking in children with CP (Bjornson et al., 2019).

Most physical therapy interventions require frequent and prolonged training, straining healthcare resources in return for modest effects on function. Therefore, it is important to explore new methods that may amplify the effects of training to maximize the potential of activity-dependent neuroplasticity elicited during physical therapy interventions.

Transcutaneous spinal cord stimulation (tSCS) is a non-invasive technique used to modulate the physiological state of the spinal cord (Gerasimenko et al., 2015). tSCS can be delivered at higher intensity levels on the surface of the skin than other surface stimulation techniques. This is due to the use of a 10 kHz stimulation waveform that effectively blocks c-fibers in the skin, allowing more current to be comfortably applied to the skin compared to traditional electrical stimulation (Gerasimenko et al., 2015). It is believed that tSCS leads to preferential activation of the Ia afferents, thereby depolarizing the motor neurons without necessarily causing direct muscle contractions (Gerasimenko et al., 2015). tSCS may also alter the excitability of intra-spinal neuronal networks, possibly by augmenting pre- and post-synaptic inhibitory mechanisms, and therefore may be a viable alternative to pharmacological and surgical approaches to manage spasticity (Barss et al., 2022). The combination of tSCS and physical therapy reduces spasticity and improves function in people with spinal cord injury (Inanici et al., 2021; Samejima et al., 2022)

The application of tSCS may also be effective in children with CP, who often have poor coordination of motor pools and a greater number of functionally aberrant connections between the brain and spinal cord (Edgerton et al., 2021; Hastings et al., 2022). tSCS may modulate sensorimotor activity to promote supraspinal-spinal connectivity required for movement and posture (Edgerton et al., 2021). Therefore, combining tSCS with treadmill training may improve walking function by modulating spinal excitability and thereby reducing spasticity in children with CP. Combining tSCS with Lokomat-based locomotor training improved walking biomechanics in children with CP (Solopova et al., 2017). Similarly, a single session of tSCS with functional task training has led to reductions in co-contraction with improved interlimb and intralimb coordination while stepping (Gad et al., 2021). tSCS and activity-based neurorehabilitation therapy improved gross motor function (Hastings et al., 2022), further suggesting that spinal networks in CP are responsive to activity-dependent plasticity (Gad et al., 2021). However, the long-term effects of tSCS when combined with task-specific training in ambulatory children with CP remain unknown. Moreover, to date there are no studies directly comparing whether the combination of tSCS and treadmill training has more functional benefits than treadmill training alone.

In this study, we investigated both short- and long-term effects of tSCS combined with locomotor training on spasticity and walking function in children with CP. We hypothesized that tSCS combined with SBLTT would lead to greater and more persistent reductions in spasticity and improved walking function, compared to SBLTT alone. To test this hypothesis, we employed a crossover design with 24 sessions of each intervention separated by an 8-week washout period. Our goal was to evaluate the effects of tSCS combined SBLTT and examine whether the combination of tSCS and SBLTT yielded greater improvements in spasticity and walking, as compared to SBLTT alone.

2.3 Methodology

This study was approved by University of Washington Human Subjects Division (IRB identifier: STUDY00008896) Children and parents were informed of the study procedures and signed the informed consent and age-appropriate assent form, respectively.

2.3.1 Study Design and Procedures

We conducted a case study with a crossover design (Figure 1A) where each participant received two interventions: Short burst interval locomotor treadmill training alone (SBLTT only), and then SBLTT combined with transcutaneous cord spinal stimulation (tSCS + SBLTT). The study began with repeated baseline measures over 4 weeks to establish participants' level of function. This was followed by 24 sessions of SBLTT only. Participants then had an 8-week washout period with no intervention to account for any long-lasting changes, prior to starting the 24 sessions of tSCS + SBLTT. After this phase, there were 3 follow-up assessments over the next 12 weeks to track long-term effects of tSCS + SBLTT. Baseline, washout, and follow-up periods did not include interventions beyond standard of care.

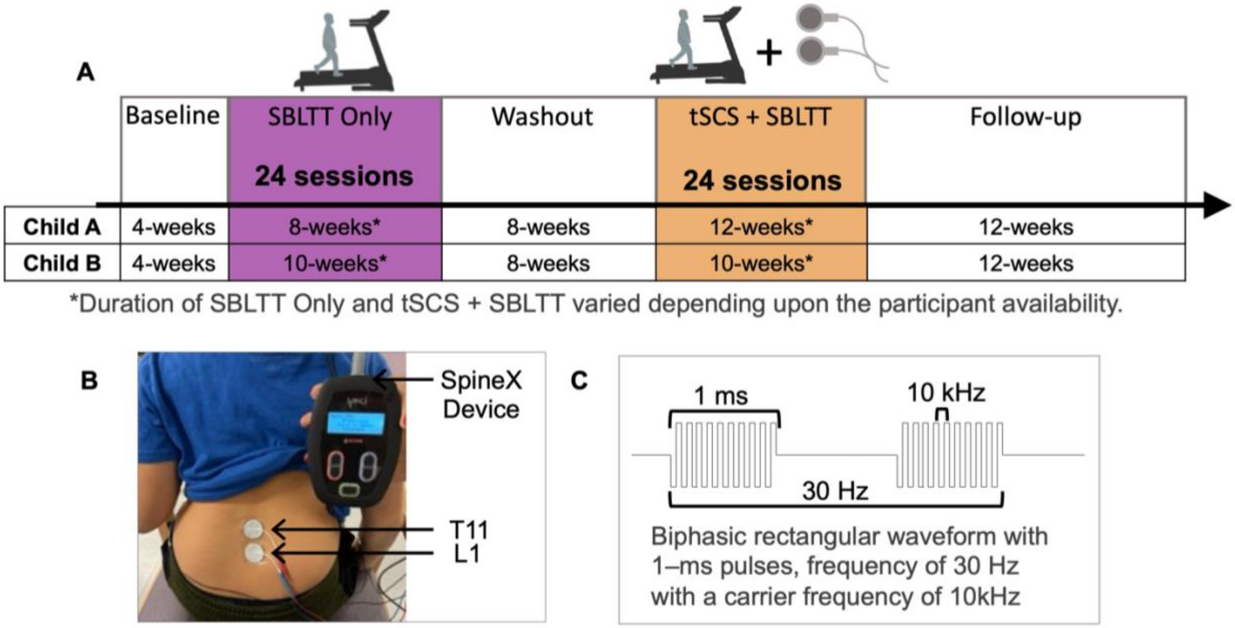


Figure 1. Experimental Design, Timeline and Procedures
(A) Study timeline for Child A and B. The duration of training periods varied between 8 to 12 weeks based upon family availability and scheduling; (B) Electrode placement and SpineX stimulator device. Electrodes were placed over the T11 and L1 vertebral level; (C) Stimulation waveform utilizing 10 kHz carrier frequency to reduce skin sensation and permit high current stimulation. SBLTT: short burst interval locomotor treadmill training; tSCS + SBLTT: transcutaneous spinal cord stimulation combined with short burst interval locomotor treadmill training.

2.3.2 Participants

We included children who had a diagnosis of spastic CP, who were ambulatory with or without assistive devices, were medically stable, cognitively capable of performing cued motor tasks, and had social support to attend the study visits. We excluded candidates who had metal implants, history of uncontrolled seizures, high-dosage regular use of botulinum toxin, or undergone selective dorsal rhizotomy surgery.

Two children with spastic diplegic CP completed the study. Parents of both children signed the informed consent for their participation in the study. Both children provided age-appropriate assent to participate in the study. The following information was collected through parent-report and clinical observation at the beginning of the study.

Child A: was a 12-year-old Caucasian male with a diagnosis of spastic diplegia with a Gross Motor Function Classification System (GMFCS) level of II. He was not currently receiving physical therapy or rehabilitation services. He was not taking spasticity medications on a regular basis; however, he used oral baclofen intermittently as needed before participating in the study, and once during the SBLTT only phase of the study. He used bilateral solid ankle foot orthoses and footwear combination for both indoor and outdoor walking.

Child B: was a 4-year-old Asian American male with a diagnosis of spastic diplegia and a GMFCS level of I. He continued his usual outpatient physical therapy for approximately 3 days/week during the study. He stopped taking baclofen 3 beginning weeks before the study and continued without medication throughout the study duration. He used bilateral ankle foot orthoses and footwear combination for outdoor walking.

2.3.3. Interventions

Both children completed 24 sessions each of SBLTT only and SBLTT + tSCS. Child A completed the SBLTT only phase in 8 weeks and the tSCS + SBLTT phase in 12 weeks due to unexpected limitations in his availability during the second intervention. Child B completed each intervention phase in 10 weeks. Training intensity and progression were tailored to each child's exertion levels in both intervention phases and were delivered by a trained physical therapist. Both children wore an ankle foot orthosis footwear combination (SFO-FC), which was prescribed by their physical therapist. Child A completed all the interventions in a laboratory setting. Child B partook in an integrated home program in which a trained physical therapist led intervention sessions in his home. Some intervention sessions and all assessment sessions took place in a laboratory setting. The integrated home program was offered to improve research access and retention for participants who could not commit to regular transit to the laboratory setting. The home program also assessed the portability of the interventions for future clinical applications. Both children used treadmill hand bars for support as needed during the training.

SBLTT Phase: During the SBLTT only phase, each intervention session included a 5-20-minute active warm-up, 30-minutes of high-intensity SBLTT, followed by a 5-minute active cool down. Rest breaks were provided as needed. SBLTT is a form of treadmill training and included alternating 30-second bursts of slow and fast walking speeds (K. F. Bjornson et al., 2019). The treadmill starting speeds were determined as 80-100% of children's overground 10-meter walking speeds, as previously reported (Bjornson et al., 2019). The fast speeds progressed within and between the intervention sessions, while the slow speeds remained constant.

tSCS + SBLTT Phase: During the tSCS + SBLTT phase, the same sequence of training, including warm-up and cool-down, was repeated with the addition of tSCS for both participants. The SCONE neuromodulation device (SpineX Inc., Los Angeles, CA, USA) was used to stimulate the spinal cord non-invasively (Gad et al., 2021). Stimulation was delivered via two 2.5 cm round electrodes (Axelgaard, ValuTrode Cloth, Axelgaard Manufacturing Co Ltd, Fallbrook, CA, USA) placed midline at T11 and L1 spinous processes as active electrodes (Figure 1B). Two 5 x 10 cm rectangular electrodes (Axelgaard, ValuTrode Cloth) were placed symmetrically over the iliac crests as the return electrodes. The stimulation waveform used biphasic, rectangular, 1-ms pulses delivered at a frequency of 30 Hz. Each pulse was filled with a carrier frequency of 10 kHz (Figure 1C). The stimulation was delivered to each location at an intensity between 20 to 60 mA for a maximum of 90 minutes by a trained physical therapist and researcher during all 24 tSCS + SBLTT intervention sessions for both children. Stimulation intensity was determined by careful observation of improved walking, such as increased knee flexion during walking and the participants' self-report of sensation of the stimulation, based on prior studies (Gad et al., 2021; Samejima et al., 2022; Solopova et al., 2017).

2.3.4 Outcomes Measures and Data Analysis

Spasticity: The Modified Ashworth Scale (MAS) was used to measure spasticity of the hamstrings, quadriceps, gastrocnemius, and soleus muscles bilaterally. The MAS is one of the most common clinical tools to evaluate the efficacy of pharmacologic and rehabilitation interventions for the treatment and management of spasticity (Mutlu et al., 2008). MAS was performed by the same trained physical therapist throughout the study. Spasticity was measured at the beginning, middle and end of each intervention phase, as well as monthly during the follow-up period.

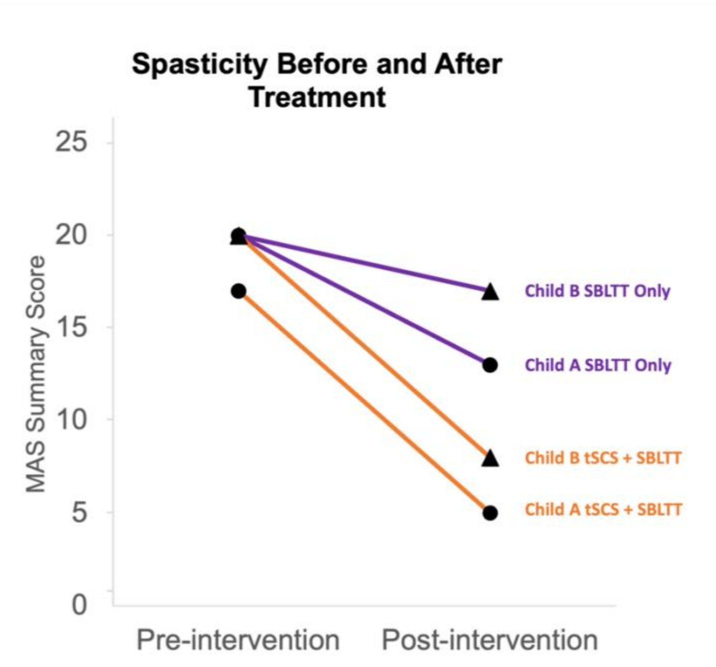
MAS scores were converted into an ordinal scale ranging from 0 to 40 for 8 muscles bilaterally, such that 0 indicates no spasticity and 40 maximum spasticity scores in all muscles. Ordinal scores were summed for each side and total score (left + right) are reported. Data were plotted to show changes in total MAS, left lower-extremity (Left LE) and right lower-extremity (Right LE) scores for each child. Ordinal scores per individual muscle group are also reported. The total spasticity scores pre- and post-SBLTT only and tSCS + SBLTT results were compared.

Walking Function and Mobility: The six-minute walk test (6MWT, for Child A) and age-appropriate (McDowell et al., 2009) one-minute walk test (1MWT, for Child B) were used as a measure of walking endurance (Fitzgerald et al., 2016; Maher et al., 2008). All tests were performed by a trained physical therapist in a gait laboratory. Greater distances walked in the 6MWT and 1MWT are indicative of more walking endurance. The timed up and go (TUG) test assessed balance, anticipatory postural control, and functional mobility, and was used as an outcome of functional mobility (Carey et al., 2016). Shorter time to complete the TUG indicates more functional mobility. We collected walking tests at least every two weeks to track participants' function throughout the study interventions. The precise timing of these tests, however, were dependent on the participants' availability to attend a testing session in our gait laboratory. Therefore, more frequent data points are available for Child A who performed all training in the laboratory, compared to Child B who received largely home training. Walking distance and functional mobility scores for pre- and post-treatment intervention timepoints were evaluated for comparison. They were also assessed longitudinally, per phase, as the average of three test trials completed on the same day for each time point. The ten-meter walk test (10MWT) evaluated walking speed during self-selected and fast walking (Thompson et al., 2008).

Data were stored and managed in Microsoft Excel (Microsoft Corporation. Microsoft Excel. 2018. Available from: https://office.microsoft.com/excel). All data analysis and plotting were performed in R studio (2021.09.2 Build 382; RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

2.4 Results

2.4.1. Spasticity: Training with SBLTT and spinal stimulation resulted in greater improvements in spasticity than SBLTT alone for both children. Spasticity summed across both extremities reduced by 5 points (15-27%) in each child during the SBLTT only phase (Figure 2). Both children's spasticity returned to near baseline levels during 8-weeks of washout (Figure 3 A and C). During the tSCS + SBLTT phase, however, spasticity reduced by 12 points (60-70%) in each child, compared to the end of the washout period. Spasticity summary scores increased by 5 points in Child A and 4 points in Child B during follow-up, remaining considerably lower than



baseline and washout scores (Figure 3 A and C).

Figure 2. Comparison of spasticity before and after each intervention. Lower extremity Modified Ashworth total summary score comparisons for pre- and post-SBLTT (purple lines) and tSCS + SBLTT (orange lines). The total spasticity summary score combines both legs and reduced by 12 points after tSCS + SBLTT for both children. Pre-Intervention scores report the end of baseline (SBLTT only) and the end of washout (tSCS + SBLTT). Post-intervention scores report the beginning of washout (SBLTT only) and beginning of follow-up (tSCS + SBLTT).

Spasticity improved in all muscles during the tSCS + SBLTT for both children, and largely persisted during three months of follow-up. The greatest improvements in spasticity were observed in the gastrocnemius (Child B) and soleus in both children following the tSCS + SBLTT phase (Figure 3B & D). The hamstrings were the only muscle group to return to baseline spasticity during follow-up (Figure 3 B and D). In addition, Child A exhibited sustained clonus of about 11 seconds in the left soleus muscle at baseline, after SBLTT only, and after washout. His clonus duration reduced to 3 seconds, clinically termed as fatigable clonus, beginning the 4th week of tSCS + SBLTT and this reduction was maintained throughout the 3-month follow-up period.

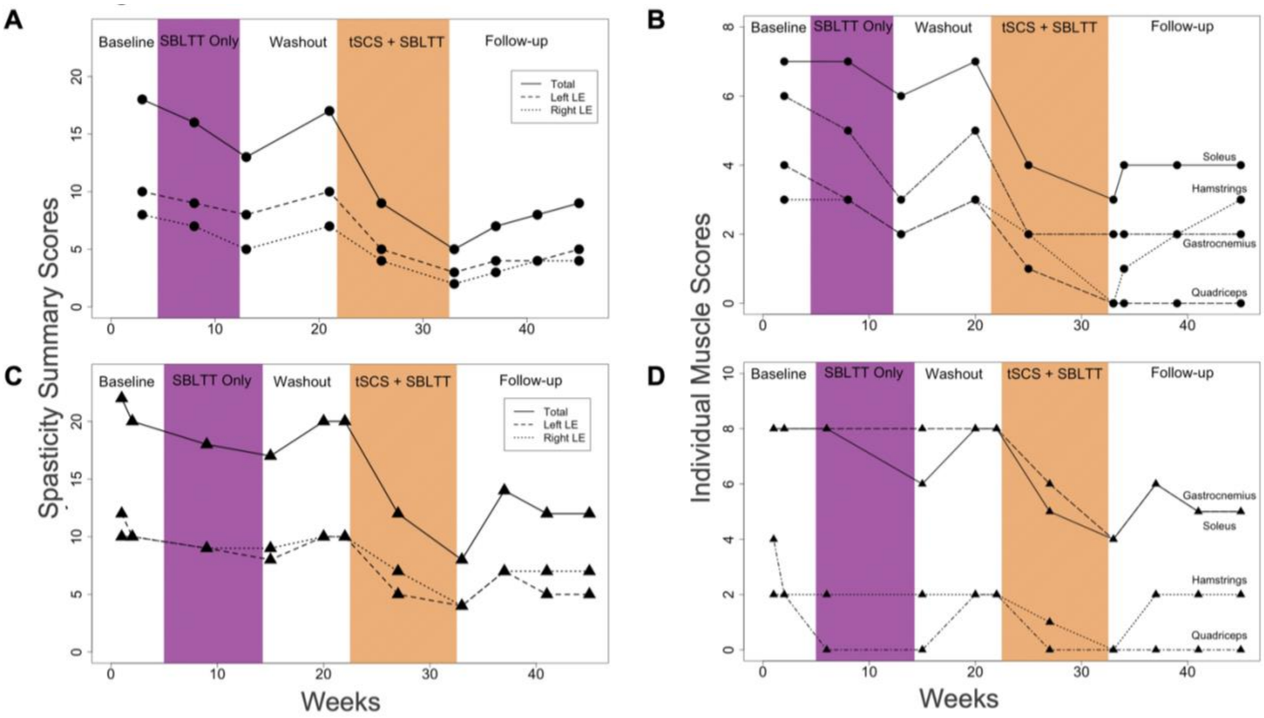


Figure 3. Spasticity trajectory throughout the study. Lower extremity Modified Ashworth Scale (MAS) results for Child A (A, B) and Child B (C, D) across all study phases. (A) and (C) indicate the MAS summary scores for each leg (dotted lines) and combined 'total' score (solid lines). (B) and (D) indicate the individual scores for each muscle group. Lower scores indicate less spasticity. SBLTT: short burst interval locomotor treadmill training; tSCS + SBLTT: transcutaneous spinal cord stimulation combined with short burst interval locomotor treadmill training; Total: The summed score of all lower-extremity muscles bilaterally; Left LE: Summed score of left lower extremity muscles; Right LE: Summed scores of right lower extremity muscles.

2.4.2 Walking Distance: Walking distance improved similarly in both children during both interventions (Figure 4A and C). Walking distances were 25% and 27% longer after SBLTT only and tSCS + SBLTT, respectively, in Child A, and 13% and 27% longer for Child B as compared to before each intervention. Walking distances remained longer for both children during follow-up (Figure 4B and D).

Figure 4

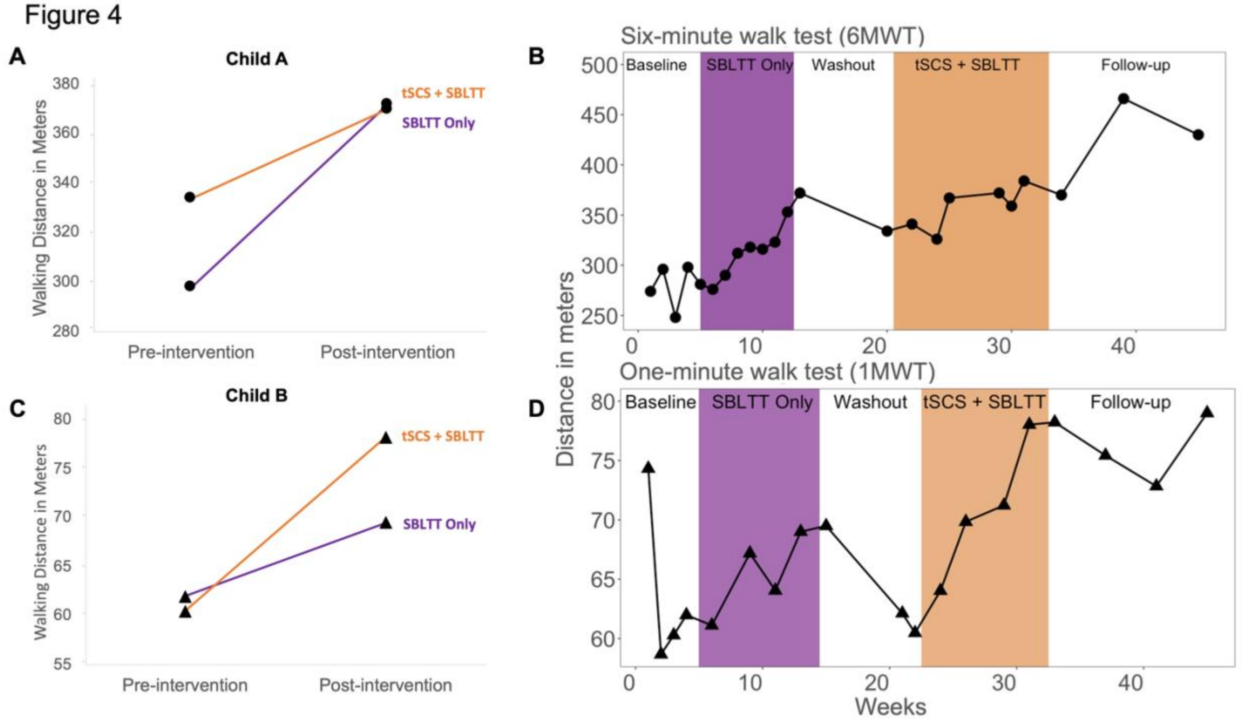


Figure 4. Walking distances as measured by the six-minute walk test (Child A) and the one-minute walk test (Child B). (A & C) Changes over each intervention comparing pre- and post-SBLTT Only (purple lines) and tSCS + SBLTT (orange lines). (B & D) Walking distance across phases for Child A and Child B, respectively. Walking distance increased during both interventions, with the longest walking distances observed at the end of tSCS + SBLTT and follow-up. SBLTT: short burst interval locomotor treadmill training; tSCS + SBLTT: transcutaneous spinal cord stimulation combined with short burst interval locomotor treadmill training.

2.4.3 Functional Mobility: The timed up and go (TUG) test revealed faster times after both intervention phases (Figure 5A). Time required to complete the TUG was 33% and 28% faster in Child A after SBLTT only and tSCS + SBLTT, respectively, compared to the end of baseline. Time was 4% and 12% faster in Child B after SBLTT only and tSCS + SBLTT, respectively, compared to the end baseline. TUG time remained lower throughout follow-up (Figure 5B and C).

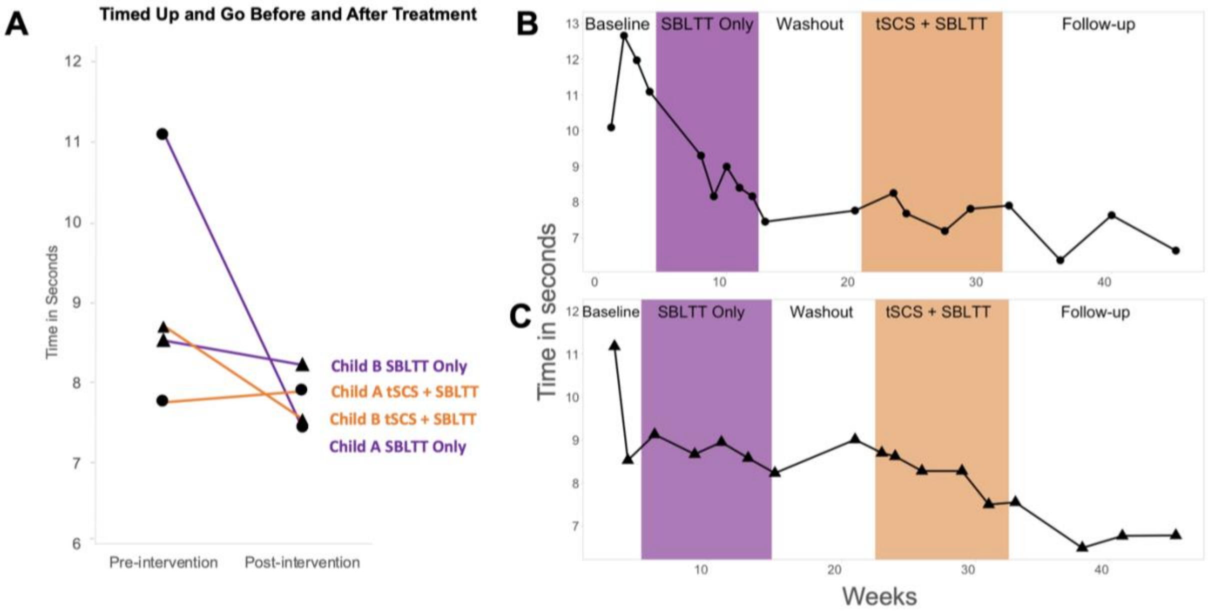


Figure 5. Mobility measures. (A) Timed Up and Go results pre- and post-SBLTT only (purple lines) and tSCS + SBLTT (orange lines). (B & C) Time taken to complete the timed-up and go test throughout the study phases for Child A and B, respectively. Time taken to complete the timed-up and go test reduced during the SBLTT Only phase, with continued improvement after tSCS + SBLTT. SBLTT: short burst interval locomotor treadmill training; tSCS + SBLTT: transcutaneous spinal cord stimulation combined with short burst interval locomotor treadmill training.

2.4.4 Walking Speed: Self-selected walking speed as measured by the 10MWT improved in both children during both SBLTT only and tSCS + SBLTT (Supplemental Figure 1). Child A walked at a self-selected speed of approximately 1.2 meters per seconds (m/s) during tSCS + SBLTT, which was greater than his self-selected speed of 1.0 m/s after SBLTT only. This speed was maintained at the end of follow-up. Child B walked at faster self-selected walking speeds in both tSCS + SBLTT and SBLTT alone phases, reaching a speed of 1.3 m/s at the end of tSCS + SBLTT and 1.4 m/s during follow-up. Child B portrayed high variability of fast walking speeds throughout the study, likely due to his younger developmental age (Supplemental Figure 1). This may also explain why Child B's self-selected and fast walking speeds were similar.

2.5 Discussion

We evaluated whether the combination of transcutaneous spinal cord stimulation and short burst interval locomotor training (tSCS + SBLTT) had greater effects on spasticity and walking function compared to SBLTT alone. Spasticity improved more than twice as much when tSCS was combined with SBLTT, as compared to SBLTT alone. Walking function improved progressively across both interventions. Improvements in spasticity and walking function were sustained throughout the 3-month follow-up period.

Sustained improvements in walking speed and endurance along with a reduction of spasticity is an important finding of this study. Typically, medications and surgical procedures that reduce spasticity often negatively affect walking function (Munger et al., 2017). For example, currently available spasticity treatments such as baclofen and selective dorsal rhizotomy improve spasticity but have controversial results on walking function (McLaughlin et al., 2002; Navarrete-Opazo et al., 2016). In this study, however, we observed better functional walking outcomes co-occurring with substantial reductions in muscle spasticity, especially following tSCS + SBLTT.

We observed similar improvements in walking function after both interventions. This suggests that SBLTT may have the potential to drive activity-dependent neuroplasticity in the brain and spinal cord by providing mass practice and repetition of moderate to high-intensity steps (K. F. Bjornson et al., 2014, 2019). The combination of SBLTT and non-invasive neuromodulation may augment long-term neuroplasticity.

The minimum clinically important difference (MCID) for the 1MWT for a child with GMFCS I spastic diplegia is 5.6 meters and 9 meters for medium and large effect size, respectively (Hassani et al., 2013). Child B's walking distance improved by 7 meters after SBLTT only and by 17 meters after tSCS + SBLTT, as compared to the end of baseline and washout periods, respectively. This exceeded the MCID for medium effect size after SBLTT only, and substantially more than the large effect size after tSCS + SBLTT (Hassani et al., 2013). This finding emphasizes the promise of intensive training or mass practice with accompanying spinal neuromodulation [33]. More modest changes were observed in TUG scores, which reached the MCID of 1.2 seconds for large effect size in Child A after SBLTT only, but not after tSCS + SBLTT. Time required to complete the TUG remained low throughout the washout period. By contrast, Child B's TUG score reached MCID of 1.1 seconds for medium effect size after tSCS + SBLTT, but not after SBLTT only (Hassani et al., 2013).

Non-invasive approaches that reorganize dysfunctional neural networks to a more functional state may be of great benefit to children with CP. Pairing spinal cord stimulation with correct proprioceptive input has the potential to reorganize the neural networks to generate coordinated movements (Edgerton et al., 2021). In concurrence with this hypothesis, we demonstrated that the combination of stimulation with SBLTT reduced spasticity and improved walking function. Transcutaneous spinal cord stimulation was well-tolerated by the children, who did not experience any adverse events. This provides additional evidence for the utility of stimulation in the pediatric population of CP (Gad et al., 2021; Solopova et al., 2017).

It is interesting to note that for Child B, the 4-year-old's first baseline test showed higher performance in walking speed and endurance, but not the timed-up-and-go test. This was perhaps a reflection of Child B's behavioral response, as he was very excited for the first day of the study, walking faster but not necessarily able to complete the TUG in less time, as that requires a more complex and coordinated sequences of activity. In addition, the higher variability in Child B’s walking speeds throughout the entire study likely reflected his younger chronological and developmental age, enthusiasm, and developing motor control.

There are several limitations to our study. First, this is a case series with only two participants, so the results are not generalizable to the greater CP population. Nonetheless, tSCS has now been studied in at least 50 children with CP across several different studies, and continues to show promising results (Gad et al., 2021; Hastings et al., 2022; Solopova et al., 2017). This is the first study, however, to show that tSCS combined with intensive treadmill training led to long-term improvements in spasticity and walking function. Second, even though therapy dosing was consistent between intervention phases, the total duration of each intervention phases was different for Child A, due to his reduced availability during the tSCS + SBLTT. To mitigate this, we provided an equal number of treatment sessions during each intervention. Further, Child B received an equal number of sessions over a consistent time period, providing evidence that the observed spasticity reductions were more likely an effect of the spinal stimulation, rather than less frequent sessions during this treatment phase in Child A. Lastly, we did not have control over the children’s activities outside of the research study. For example, Child A returned to in-person school during the stimulation phase, and Child B continued outpatient physical therapy throughout the study. However, this may show that even when the interventions are applied in the real-world context of changes to daily life, tSCS + SBLTT consistently resulted in greater improvement of spasticity compared to SBLTT only.

2.6 Conclusion

We found that the combination of transcutaneous spinal cord stimulation (tSCS) and short burst interval locomotor treadmill training (SBLTT) is well-tolerated and markedly improves spasticity for two children with CP. This is the first study to show that the combination of high-repetition, task-specific training (i. e. SBLTT) and tSCS leads to greater reductions in spasticity, with continued improvements in walking and mobility, compared to training alone. SBLTT therapy intensity and progression were similar in both intervention phases, suggesting an additional benefit of tSCS when combined with intensive treadmill training. To determine clinical utility and translatability of spinal cord stimulation, future work should focus on studying a larger sample with randomized treatment groups and blinded assessors, with the goal of improving walking function and community ambulation for children with CP.

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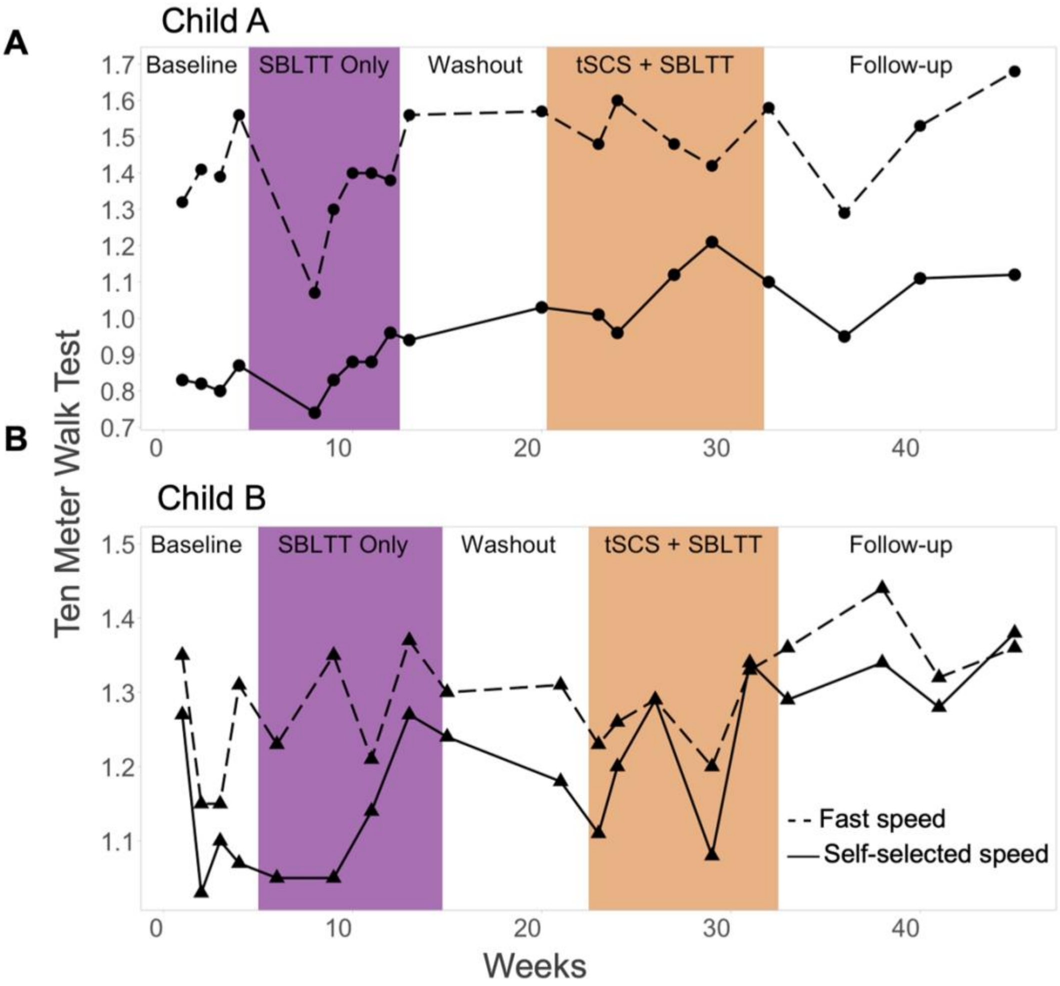
Supplemental Figure



Supplementary Figure 1. Ten-meter walk test trajectory for self-selected and fast walking speeds for (A) Child A and (B) Child B. Self-selected walking speeds improved during the SBLTT only phase and remained higher during tSCS + SBLTT in both children. Fast walking speeds were more variable in both children. SBLTT: short burst interval locomotor treadmill training; tSCS + SBLTT: transcutaneous spinal cord stimulation combined with short burst interval locomotor treadmill training.

Chapter 3. Effects of Spinal Neuromodulation and Short Burst Interval Locomotor Treadmill Training Across ICF Domains in Children with Cerebral Palsy

3.1 Abstract

3.1.1 Purpose: To evaluate the effects of short burst interval treadmill training (SBLTT), and the combination of transcutaneous spinal cord stimulation (tSCS) and SBLTT on spasticity, walking function and mobility across ICF domains.

3.1.2 Methods: Each participant first received SBLTT only followed by tSCS + SBLTT in a cross-over study design. There was an 8-week washout between the two interventions and a 12-week follow-up at the end of tSCS + SBLTT.

3.1.3 Results: Spasticity measured by MAS scores reduced by 21% after SBLTT only and by 68% after tSCS + SBLTT. 38% reductions were observed in Tardieu scores after SBLTT only, and 60% after tSCS + SBLTT. Walking distance, speed, functional mobility and dynamic balance improved after both interventions. Improved spasticity and walking function were sustained for at least 3-months during the follow-up period.

3.1.4 Conclusion: The combination of tSCS and SBLTT leads to substantial reduction in spasticity with continued improvements in walking function and mobility.

Introduction

Cerebral Palsy (CP) is the most common childhood motor disorder (Accardo & Capute, 2008), which is characterized by muscle weakness, impaired coordination of muscles and spasticity

(Poon & Hui-Chan, 2009). CP is caused by damage to the developing brain before, during or after birth. Even though CP is termed as a non-progressive disorder, its consequences can lead to progressive limitations in function as children grow into adulthood. CP affects children’s motor function, causes challenges related to mobility and walking, and leads to participation restrictions in recreational activities such as sports (Øtensjø et al., 2004).

Spasticity and muscle weakness are common manifestations of CP. About 70% of children with CP present with spasticity (Westbom et al., 2007), making spastic CP the most common subtype. Current spasticity management options include the use of medication and surgical procedures. Baclofen is a common medication that can be taken orally or delivered through a pump (Navarrete-Opazo et al., 2016). Selective dorsal rhizotomy is a surgical procedure which transects the spinal sensory nerve roots that contribute to spasticity (Abbott, 2020). Botulinum Toxin type-A is a neurotoxin that can be delivered locally at the muscle to reduce spasticity (Multani et al., 2019). The evidence on long-term functional effects of these spasticity management approaches, however, is inconclusive (MacWilliams et al., 2022; Tedroff et al., 2020).

World Health Organization’s (WHO) International Classification of Functioning, Disability and Health (ICF) framework provides a holistic view of the person, weighs intricacies of functioning, presents a unified language, and offers a direct insight into functioning. It describes bidirectional relationships between body structure and function, such as spasticity, and activity and participation, such as walking and community ambulation (World Health Organization, 2002).

ICF puts more emphasis on activity and participation than body structure and function, highlighting the importance of targeting physical therapy interventions that impact children's activities and participation in life. WHO strongly suggests that scientific research should utilize the ICF to structure interdisciplinary research in disability to make results of research comparable to what individuals with disabilities do in their daily life (World Health Organization, 2002).

Approximately 40% of children with CP have limitations in walking, running, and playing (Boulet et al., 2009). They have less intense walking activity compared to their typically developing peers (Bjornson et al., 2007), which increases their likelihood of secondary musculoskeletal complications as children transition into adulthood (Gajdosik & Cicirello, 2002). Walking performance decreases as children with CP grow older (Bjornson et al., 2020). Physical therapy is a front-line treatment to enhance function for people with CP. Physical therapists focus on functional limitations and tailor therapeutic exercises to improve functional outcomes. Physical therapy programs aim to harness neuroplasticity to provide long-lasting gains in function that facilitate children's participation and improve their quality of life.

Physical therapy management of CP utilizes high-repetition, task-specific exercises (Damiano, 2006). There is an emphasis on promoting activity through intensive active training protocols, lifestyle modifications and mobility-enhancing devices (Damiano, 2006). High-dosage of whole-task practice, such as stepping, is essential to achieve functional goals such as walking (Jackman et al., 2022). Evidence suggests that the whole tasks need to be practiced, ideally within a real-world context, in order to be transferred to individual’s daily life and improve function (Mastos et al., 2007). Children have a remarkable capacity for plastic change compared to adults (Takesian & Hensch, 2013). These factors highlight the importance of challenging children with CP with high intensities and dosages of targeted behavior, such as walking, and through different environmental enrichments such as clinical laboratories and the outdoor communities.

International clinical practice guidelines recommend utilizing treadmill training to improve walking speed and endurance in children with CP who are at a GMFCS level I-III (Jackman et al., 2022). Treadmill training provides high repetition of steps in a relatively safe manner, and improves walking function (Grecco et al., 2013b; Hornby et al., 2005; Macko et al., 2001; Schindl et al., 2008; Westlake & Patten, 2009). While more exclusive options such as body-weight support training are available, traditional full weight-bearing treadmill training has the greatest effect on walking speed, postural stability, and functional balance in children with CP (Grecco et al., 2013a; Moreau et al., 2016). Traditional treadmill training programs, however, are based on adult’s walking patterns and focus on steady-state walking (Hicks & Martin Ginis, 2008; Laufer et al., 2001; Polese et al., 2013; Westlake & Patten, 2009). Programs that are based on children’s natural walking patterns, which include short bursts of activities that replicate real-world mobility, may produce long-lasting functional gains in children. Short burst interval locomotor training (SBLTT) is a specialized training that is based on children’s natural walking patterns. Children walk with alternating bursts of high and low speeds for 30 seconds each over total of 30-minutes per session (Bjornson et al., 2011). SBLTT allows for specificity of training, repetition, intensity, transference, and interference, and therefore may have the potential to drive neuroplasticity (Nahum et al., 2013). It improves walking capacity measured by speed, endurance and mobility, and community walking performance (Bjornson et al., 2019).

Non-invasive neuromodulation has the potential to magnify functional gains of rehabilitation interventions. Transcutaneous spinal cord stimulation (tSCS) is one such neuromodulation technique that has shown promising preliminary results in people with spinal cord injuries. Early studies demonstrate that the combination of tSCS and task-specific exercises such as hand therapy and gait training lead to improvements in motor function (Inanici et al., 2018, 2021; Samejima et al., 2022). People with spinal cord injuries have gained 3-fold grip strength and have walked three times longer distances after combination of tSCS and task-specific therapy (Gad et al., 2018; Samejima et al., 2022). In CP, a single-session of tSCS when paired with task-specific activity led to stepping-like pattern in a child who was unable to step before (Gad et al., 2021). An 8-week tSCS and activity-based neurorehabilitation training program led to improved motor function and quality of life in sixteen children with CP (Hastings et al., 2022). Literature also suggests that the combination of tSCS with task-specific training may have added functional benefits over training alone (Inanici et al., 2018, 2021; Samejima et al., 2022; Solopova et al., 2017). For example, in children with CP, Lokomat based training program combined with tSCS led to better motor outcomes than Lokomat training alone (Solopova et al., 2017).

Taken together, prior studies suggest the greatest benefits to motor function when tSCS is combined with task-specific training. An open question, however, is whether changes in motor function will translate into children’s daily life. There is currently no evidence on the long-lasting effects of tSCS combined with task-specific training for children with CP. The end goal of rehabilitation interventions is to make the child more independent to improve their engagement, integration, and participation in daily life. It is imperative that rehabilitation interventions have a positive impact on children's quality of life. Therefore, it is also important that clinical research includes outcome measures that are comprehensively evaluating function, participation, and quality of life. Moreover, it is important to understand children and parents' perspectives about the effects of interventions, therefore making self-reported outcome measures of great value in clinical research.

We conducted a pilot single-subject case study to evaluate the effects of the combination of tSCS and SBLTT across ICF domains of body structure and function, activity and participation. We aimed to understand whether the combination of tSCS and SBLTT led to better and long-lasting outcomes than SBLTT alone.

3.2 Methods

3.2.1 Study Design and Procedures

All study procedures were approved by the University of Washington Institutional Review Board (IRB # Study 00008896) and were registered with Clinical Trials.gov (NCT04467437). We conducted a prospective crossover study with two intervention arms. This study design was selected to measure the effects of SBLTT, and to further evaluate whether tSCS has an additive effect over SBLTT alone.

The study started with a 4-week repeated baseline period. Each participant then received short burst interval locomotor training only (SBLTT only) . This was followed by an 8-week washout period with no intervention beyond children's standard of care. Then, the participants received transcutaneous spinal cord stimulation combined with SBLTT (tSCS + SBLTT). There was a 12-week follow-up at the end to evaluate long-term effects of tSCS + SBLTT.

All intervention sessions began with 5–15 minutes of active warm-up activities, followed by 30 minutes of SBLTT on a treadmill. The study visit concluded with 5–15 minutes of active cool down. Warm-up and cool-down activities were tailored to participant's play preferences and were led by a trained physical therapist with contact guard or stand-by assist, as appropriate. Training sessions were conducted in the Amplifying Movement and Performance laboratory at University of Washington for three out of four participants. One participant chose to participate in an integrated home program in which most training sessions with and without stimulation were conducted at home. All assessments and 1 session per week were conducted in the laboratory by a trained physical therapist and researcher.

During both treatment phases, SBLTT was delivered for 30 minutes each day and consisted of 30-seconds of alternating slow and fast speeds. Slow speeds remained constant throughout the treatment phase, whereas fast speeds were progressed within and between sessions based on the children's improved function as follows. Children's OMNI scale was collected every 5-minutes to understand level of exertion during SBLTT (Fragala-Pinkham et al., 2015). The OMNI scale of perceived exertion is a clinically feasible measure to monitor exercise intensity in ambulatory children and adolescents with CP. Progressions in fast speed were made based on children's OMNI scores and clinical judgement by a physical therapist. Any occurrence of tripping of stumbling was taken into consideration for progression-related decision-making. Rest breaks were offered based on OMNI and clinical signs of tiredness such as flushed face, excessive sweat, inability to walk and talk, and behavioral signs such as temperament and emotional regulation.

During the tSCS + SBLTT intervention phase, tSCS was delivered at T11 and L1 vertebral levels using two 2.5 cm round electrodes (Axelgaard, ValuTrode cloth) based on prior studies (Gad et al., 2017, 2021; Hastings et al., 2022; Samejima et al., 2022). These round electrodes served as cathodes. Two 5 x 10 cm rectangular electrodes (Axelgaard, ValuTrode cloth) were placed symmetrically over bilateral iliac crests as anodes. The stimulation waveform used biphasic, rectangular, 1 ms pulses at a frequency of 30 Hz, filled with carrier frequency of 10 kilohertz (kHz). A portable tSCS stimulator (SCONE, SpineX, inc.) delivered the stimulation during treadmill training.

Stimulation current amplitude was set to a sub-threshold intensity that did not cause muscle activation. The goal was that participants voluntarily initiate and control movements. Amplitude was also determined based on children's self-report of quality of walking, sensation around the cathodes, and a physical therapist's observation and clinical judgement of gait quality and participant's emotional behavior.

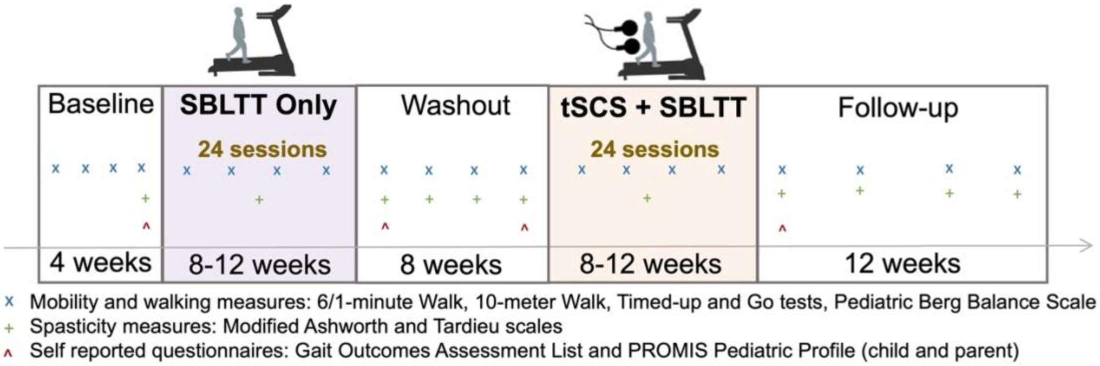


Figure 1. Study phases and assessment timepoints with 24 intervention sessions in each treatment phase. Duration of intervention phases dependent on children and family's availability. SBLTT only: short burst interval locomotor treadmill training; tSCS + SBLTT: spinal stimulation combined with SBLTT.

3.2.2 Outcome measures

Primary Outcomes

Spasticity and walking function were primary outcomes of interest.

Spasticity. Spasticity was measured by the Modified Ashworth (MAS) and Tardieu Scales. Both MAS and Tardieu are psychometrically sound clinical measures of spasticity (Alhusaini et al., 2010; Mutlu et al., 2008) that have been widely used to measure efficacy of spasticity management interventions (Buizer et al., 2019; Davidson et al., 2020; Pruszczynski et al., 2018; Tedroff et al., 2020; Zaino et al., 2020). Hamstrings, quadriceps, gastrocnemius, and soleus muscles were evaluated bilaterally. For Tardieu, stretching at a slow velocity of V1 and stretching as fast as possible, or V3, were applied to measure R2 and R1 angles, respectively. R1 represents an angle of catch, where a sudden increase of muscle resistance is felt during a fast passive stretch. R2 is an angle indicating the tested muscle length at a slow passive range of motion (Shu et al., 2021). The quality of muscle reaction was graded at the stretching velocity of V3.

Walking Function. Walking function was evaluated by measures of distance, speed, functional mobility. Walking distance was measured by the 6- or 1-minute walk tests (6-/1-MWT), valid measures of walking distance and endurance in children and youth with CP (Brona C et al., 2005; Maher et al., 2008; McDowell et al., 2009; Stockman, 2009). S01 completed the 6-minute walk test. S01's 6-minute walking distance was normalized to 1 minute by dividing the walking distance by 6 for the purposes of data visualization. S02, S04 and S05 completed the 1MWT. Walking speed was measured by the self-selected and fast 10-meter walk test (10MWT). 10MWT is an objective and valid measure of walking speed that is predictive of community ambulation (Beckung & Hagberg, 2007; Pirpiris et al., 2003, 2006). Functional mobility was measured using the Timed up and Go test (TUG). TUG is a reliable performance-based test to quantify functional mobility that utilities coordination, motor planning and dynamic balance (Carey et al., 2016b; Hafsteinsdóttir et al., 2014; Hassani et al., 2013). 1MWT, self-selected and fast 10MWT and TUG were repeated three times at each assessment.

Secondary Outcomes

Gait Outcomes Assessment List and Patient Reported Outcomes Measurement Information System pediatric profile self-reported questionnaires were used as a measure of gait priorities and perceived overall health, respectively.

Gait Outcomes Assessment List (GOAL). GOAL assesses self-reported gait priorities and functional mobility for ambulatory children with CP (Davids, 2018). It is a meaningful outcome that can discriminate between gross motor functional levels and correlates with standard functional assessments and gait analyses (Thomason et al., 2018). It is one of the very few measures of gait that provides comprehensive assessment across all ICF domains (Thomason et al., 2018). We used both child and parent versions of both the questionnaires to mutually understand children and parent’s perspectives. Children and parents filled in the questionnaires before and after each treatment phase. GOAL-Child data were not collected from S02 due to his younger age and still-developing literacy skills. PROMIS-Parent data was not collected from S01’s parent due to pending IRB approval to add this measure.

Both versions of GOAL consist of 48 items, grouped into 7 domains as follows: activities of daily living and independence; gait function and mobility; pain, discomfort and fatigue; physical activities, sports and recreation; gait pattern and appearance; use of braces and mobility aids; body image and self-esteem (Thomason et al., 2018).

<u>PROMIS Pediatric Profile.</u> PROMIS pediatric profile–49 instrument is a collection of short forms on health-related quality of life. It was used to assess six domains: depressive symptoms, anxiety, physical function–mobility, pain interreference, fatigue and peer relationships, along with a single item on pain intensity. PROMIS has shown moderate to high correlations with performance-based measures of mobility (DeWalt et al., 2015; Kratz et al., 2013).

Figure 2 represents outcome measures in the context of the ICF framework.

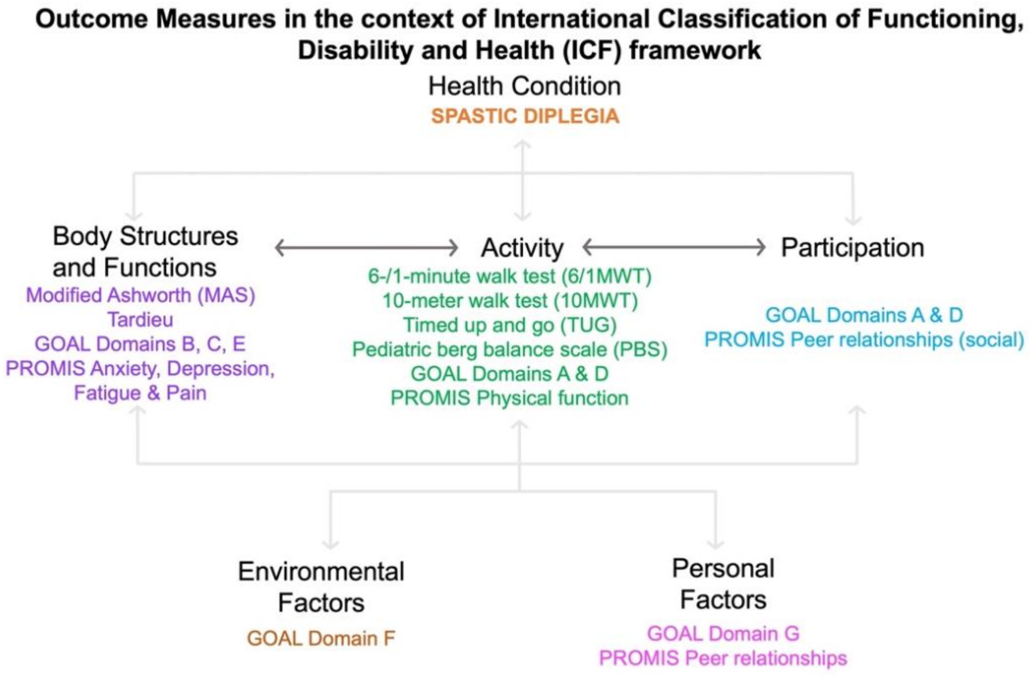


Figure 2. Outcomes in the context of the ICF model.

3.2.3 Participants, Inclusion and Exclusion Criteria:

Specific Inclusion and exclusion criteria are reported in Table 1. Four children who satisfied all the inclusion and exclusion criteria participated in the study.

Inclusion Criteria	***Exclusion Criteria***
Diagnosis of spastic CP	History of or active uncontrolled seizures
Ambulatory with or without assistive devices	Metal implants, such as cardiac pacemakers
Between 4-18 years of age	Selective dorsal rhizotomy in the past
Stable medical condition to participate in physical activity and training	Botox/neurotoxins in the past 6 months
Self-reported social support for participation	Had an orthopedic surgery in past 12 months

Table 1. Inclusion and Exclusion criteria.

3.2.4 Data Processing, Analysis and Visualization

Data were stored and managed in Microsoft Excel (Microsoft Corporation. Microsoft Excel. 2018. Available from: https://office.microsoft.com/excel). All data analysis and plotting were performed in R studio (2021.09.2 Build 382; RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

For evaluating spasticity, MAS scores were converted into an ordinal scale (Inanici et al., 2021; Samejima et al., 2022) ranging from 0 to 40 for 8 muscles bilaterally, such that 0 indicates no spasticity and 40 maximum spasticity scores in all muscles for each participant. Ordinal scores were summed to report total scores. Data were plotted to show changes in total MAS for each child. Tardieu scores were summed so that 0 indicates no spasticity and 40 maximum spasticity scores in all muscles. Pooled total MAS and Tardieu spasticity scores pre- and post-interventions were compared to explore changes in spasticity over the course of each intervention. All mobility and walking function measures were plotted to visualize any trends per phase. Pooled pre- and post-intervention scores were summed for comparison. Shapiro-Wilk test was conducted to evaluate whether the data were normally distributed. T-tests were conducted on MAS and Tardieu pooled total data points to compare whether the effects of SBLTT and tSCS + SBLTT were statistically significant.

Statistical analysis was conducted on pooled data from four participants to compare whether the 1MWT, self-selected and fast 10MWT, and TUG walking test data were significantly different before and after each intervention. Shapiro-Wilk normality test was performed to check for the distribution of the data. For the walking tests where the data were normally distributed, paired T-tests were conducted. For data that were not normally distributed, paired Wilcoxon signed-rank tests were used.

Self-reported measures from children and parents were evaluated separately. GOAL data was entered into a formula-protected Microsoft Excel 2013 spreadsheet provided by GOAL developers, and scoring was performed automatically using this spreadsheet. The maximum GOAL score is 100 and a higher score equates higher function. Standardized domain and total scores were calculated for each participant. For child- and parent-reported PROMIS pediatric profile–49, raw data were examined for trends for each domain.

3.3 Results

Five participants consented to participate in the study. One participant, S03, withdrew from the study prior to baseline assessments due to personal reasons. Four children with spastic diplegia completed 24 sessions of SBLTT only and 24 sessions of tSCS + SBLTT. Data from these four participants are included for the final analyses. Their demographics are listed in Table 2.

ID	***Age (years)***	***Gender***	***Diagnosis***	***GMFCS Level***	***Assistive/Mobility Device***
S01	12	Male	Spastic diplegia	II	Bilateral AFO-FC
S02	4	Male	Spastic diplegia	I	Bilateral AFO-FC
S04	10	Male	Spastic diplegia	II	Bilateral AFO-FC
S05	13	Male	Spastic diplegia	I	Shoe insert on left side due to leg length discrepancy

*AFO-FC Ankle foot orthosis–footwear combination

Table 2. Demographic and clinical characteristics of participants

Stimulation was well tolerated by all participants. Participants described the sensation of stimulation as a massage or tapping. There were no side effects or adverse events during or after tSCS.

3.3.1 Spasticity

Spasticity reduced after each intervention, with greater reductions observed after tSCS + SBLTT. Specifically, MAS scores reduced by an average of 14 +/- 1.7 points (21%) after SBLTT only and by 45 +/- 1.9 points (68%) after tSCS + SBLTT (Figure 3). The mean reduction after tSCS + SBLTT was approximately 2.5 times greater than SBLTT only. Spasticity trended toward a reduction during SBLTT but the results were not significant (t(3) = -2.25, p = 0.110; Cohen's d = -1.30, 95% CI [-2.75, 0.25]). Following tSCS + SBLTT, however, spasticity was significantly reduced (t(3) = -13.17, p < .001; Cohen's d = -7.61, 95% CI [-13.52, -1.89]).

Similarly, measurements of spasticity based on the Tardieu scale were approximately 2 times greater after tSCS + SBLTT compared to SBLTT only. Tardieu scores reduced by 17 +/- 3.8 points (38%) after SBLTT only and by 24 +/- 1.4 points after tSCS + SBLTT (60%). . T-tests revealed that reductions in spasticity trended towards significance for SBLTT only (t(3) = -2.85, p = 0.065; Cohen's d = -1.64, 95% CI [-3.28, 0.09]) and tSCS + SBLTT (t(3) = -2.78, p = 0.069; Cohen's d = -1.60, 95% CI [-3.22, 0.11]).. Spasticity improvements were maintained for three months after tSCS + SBLTT.

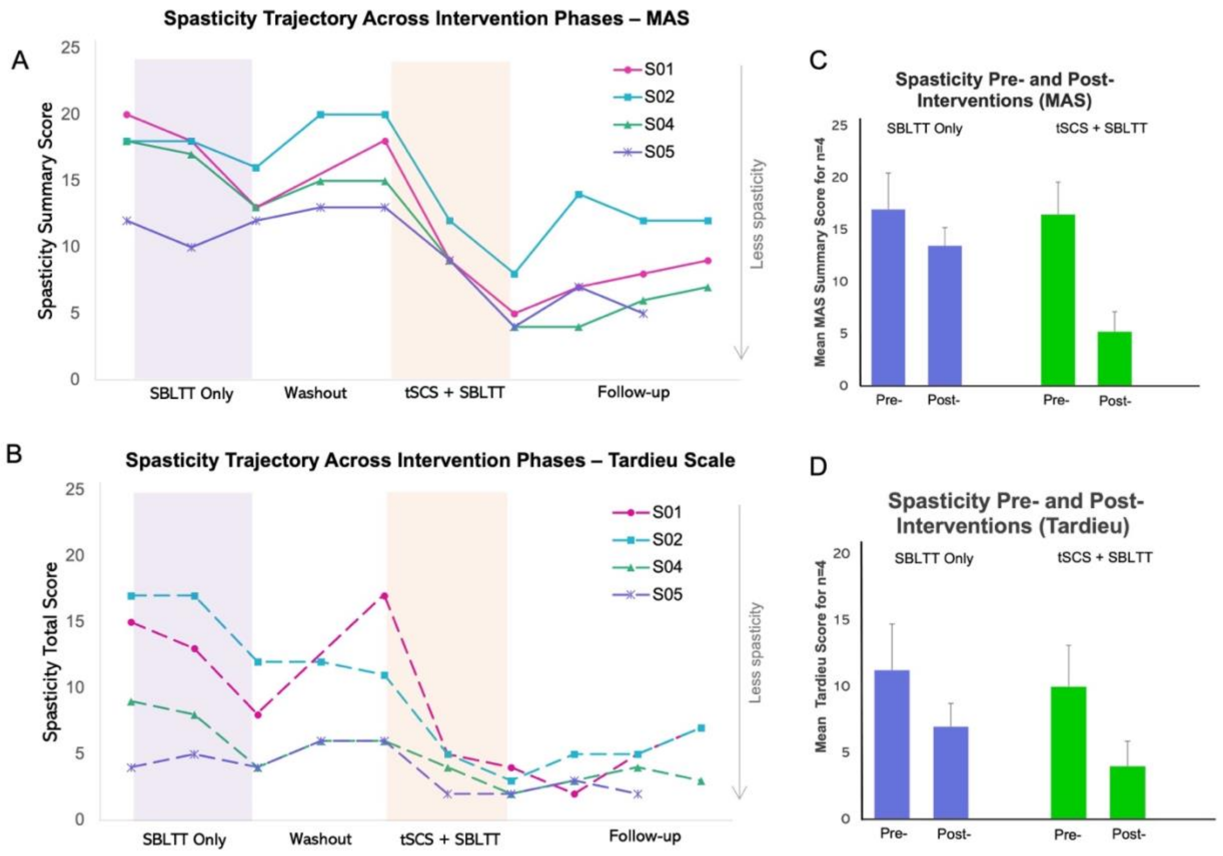


Figure 3. Consistent reductions in spasticity observed after each intervention, with considerably more reductions during tSCS + SBLTT. Spasticity trajectories were measured by (A) Modified Ashworth (MAS) and (B) Tardieu scales. Comparison of the average change in each spasticity measure for n=4 participants before and after each intervention (C, D).

3.3.2 Walking Function

Walking function was quantified using measures of distance, self-selected and fast speeds, and Timed Up and Go (TUG) time.

Both interventions led to similar and significant increases in walking distance (Figure 4A). SBLTT training improved walking distance by 14 meters (V = 45, p-value = 0.004; Wilcoxon Signed-Rank test), while tSCS + SBLTT increased walking distance by an additional 10 meters (V = 45, p-value = 0.004) (Figure 4B). Walking distance increased further during the threemonth follow-up for S01 and S04 and was maintained for S02 (S05 data pending collection; Figure 4A).

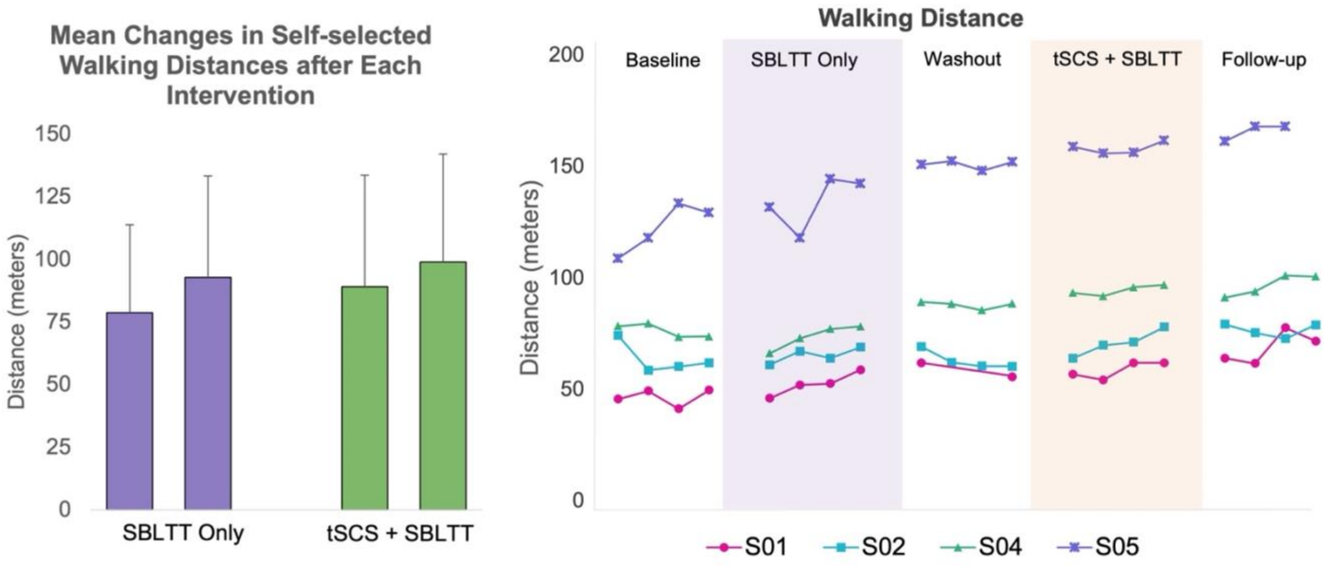


Figure 4. Walking distance improved during each intervention. (A) trajectory of walking distances across study phases for each participant. (B) Average walking distance from n=4 participants before and after each intervention, SBLTT only and tSCS + SBLTT.

There was a trend toward improvement in self-selected walking speeds after both SBLTT only and tSCS + SBLTT (Figure 5A). The pre- and post-intervention comparisons for self-selected walking speeds were not significant for SBLTT only (t(11) = 0.29, p = 0.779; Cohen’s d = 0.09, 95% CI [-0.51, 0.68]) and trended toward significance after tSCS + SBLTT (t(11) = 2.18, p = 0.052; Cohen’s d = 0.66, 95% CI [-4.71e-03, 1.30]), as represented in Figure 5B.

Pooled mean fast speed increased by 0.06 meters/second after SBLTT only and by 0.16 meters/second after tSCS + SBLTT (Figure 5D). The Wilcoxon Signed-Ranks test revealed that the post-intervention fast speeds were higher than pre-intervention but not significant for both SBLTT only (V = 56.5, p-value = 0.18), and tSCS + SBLTT (V = 57, p-value = 0.17).

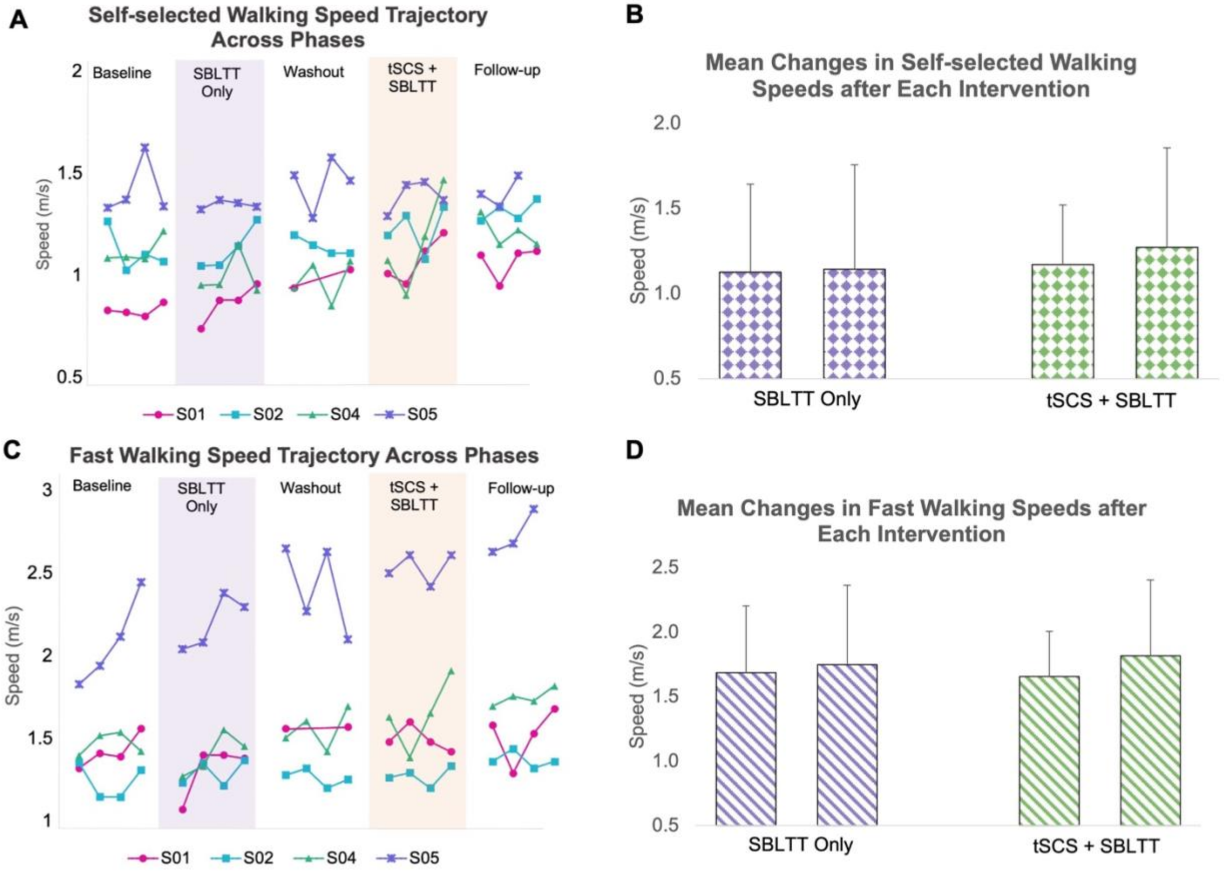


Figure 5. Improvements in self-selected and fast walking speeds after each intervention. Trajectories of walking self-selected (A) and fast (C) walking speeds across study phases for each participant are presented. B and D presents the pooled mean change in walking speeds from n=4 participants after each intervention, SBLTT only (purple) and tSCS + SBLTT (green).

Functional mobility was measured using the Timed Up and Go test (TUG) and revealed significant improvements during both interventions (Figure 6A). Time to complete TUG reduced by 1.05 seconds after SBLTT only (t(11) = -3.18, p = 0.009; Cohen's d = -0.96, 95% CI [-1.65, -0.23]), and by 0.40 seconds after tSCS + SBLTT (t(11) = -3.10, p = 0.010; Cohen's d = -0.94, 95% CI [-1.63, -0.21]) (Figure 6B). A reduced time to complete the TUG indicates more functional mobility. Additional walking function results are presented in Supplemental Table 1.

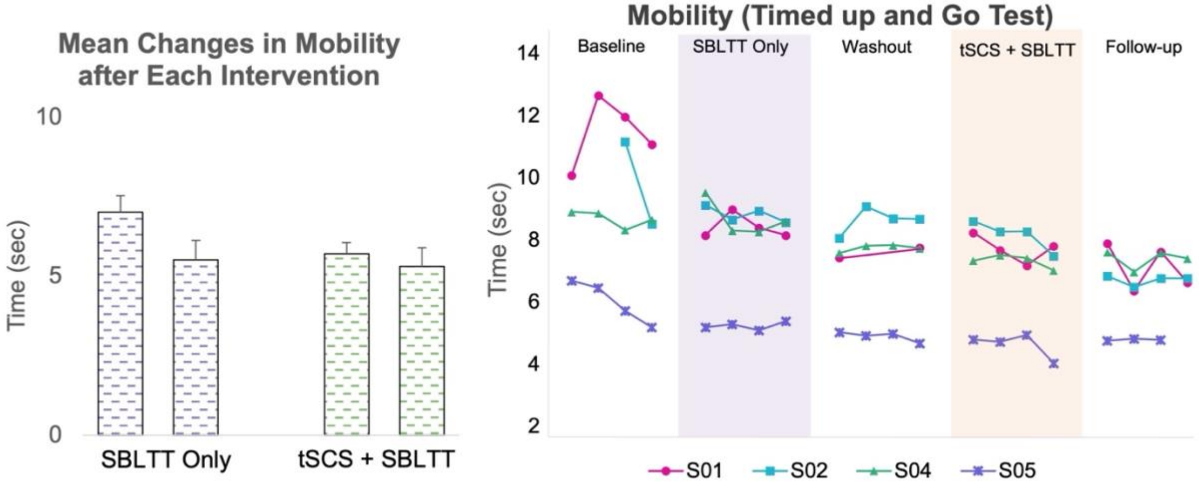


Figure 6. Consistent reductions in time to complete the Time Up and Go (TUG) test after each intervention. (A) TUG times across study phases for each participant. (B) pooled mean + SD change in TUG times, from n=4 participants after each intervention, SBLTT only (purple) and tSCS + SBLTT (green).

3.3.3 GOAL

GOAL-Child and GOAL-Parent self-reported questionnaires were used to measure gait priorities and functional mobility. Children completed the child version of the questionnaire, while parents completed the parent version.

There was a consistent trend of increase in total GOAL scores after tSCS + SBLTT for both children and parents. Self-reported GOAL-Child scores increased by an average of 10 +/-3.61 points (14%) after tSCS + SBLTT. After SBLTT only, however, we observed average 4 +/- 7.55 point (5%) decrease in total GOAL scores (Figure 7-A).

Self-reported GOAL-Parent scores were fairly stable but trended in the same direction as the child scores across both interventions. Specifically, they reduced by an average of 1.75 points (2.63%) after SBLTT only and by 3 points (4.60%) after tSCS + SBLTT (Figure 7-B).

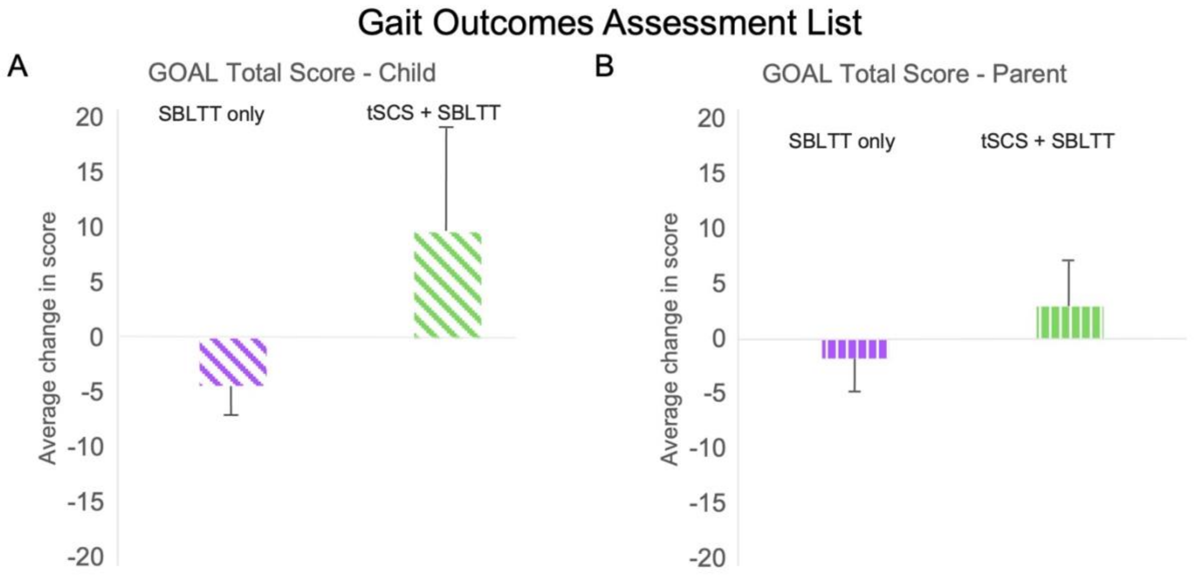


Figure 7. Changes in Gait Outcomes Assessment List (GOAL) total scores after SBLTT only and tSCS + SBLTT are presented as reported by children (A) and parents (B).

There was a remarkable trend in GOAL-Child Domain E: Gait Pattern and Appearance. All children reported an increase in Domain E scores after both interventions (Figure 8-A). Domain E scores increased by an average of 14 +/-7.6 points (21.99%) after SBLTT only and by 12.6 +/-9.8 points (20.43%) after tSCS + SBLTT. Domain E-Parent scores improved by an average of 4 +/-7.6 points (8.70%) after SBLTT only and by 5 +/-9.8 points (9.07%) after tSCS + SBLTT (Figure 8B).

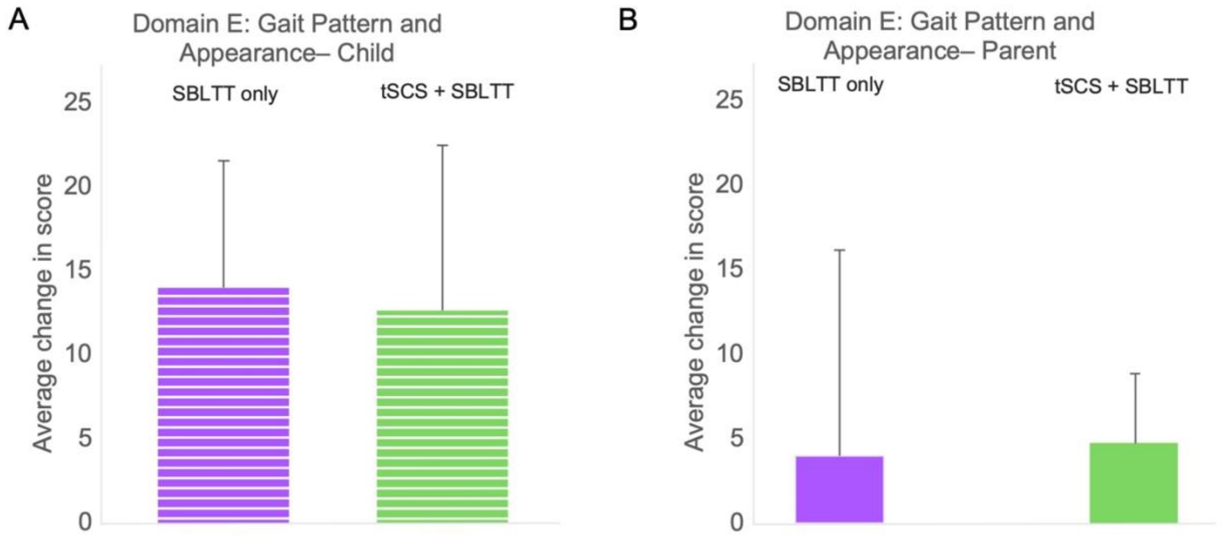


Figure 8. Changes in Gait Outcomes Assessment List (GOAL): Domain E Gait Pattern and Appearance average scores after SBLTT only and tSCS + SBLTT are presented as reported by children (A) and parents (B).

There were rather inconsistent trends in Domains A, B, C, D, F and G for both GOAL-Child and GOAL-Parent. These are presented in Supplemental tables 2 and 3

3.3.4 PROMIS

PROMIS was used to assess six health-related quality of life domains: depressive symptoms, anxiety, physical function–mobility, pain interreference, fatigue, peer relationships, and pain intensity. Consistent trends were only observed in the Fatigue domain. Children reported more fatigue after completing SBLTT, but little change after tSCS + SBLTT (Figure 9-A). In contrast, all parents consistently reported less fatigue after tSCS + SBLTT. Specifically, S02 and S05's parent reported a 4-point reduction in fatigue after tSCS + SBLTT, while S04's parent reported a 1-point reduction in fatigue (Figure 9-B). We observed inconsistent trends in other PROMIS domains. These are presented in Supplemental table 4.

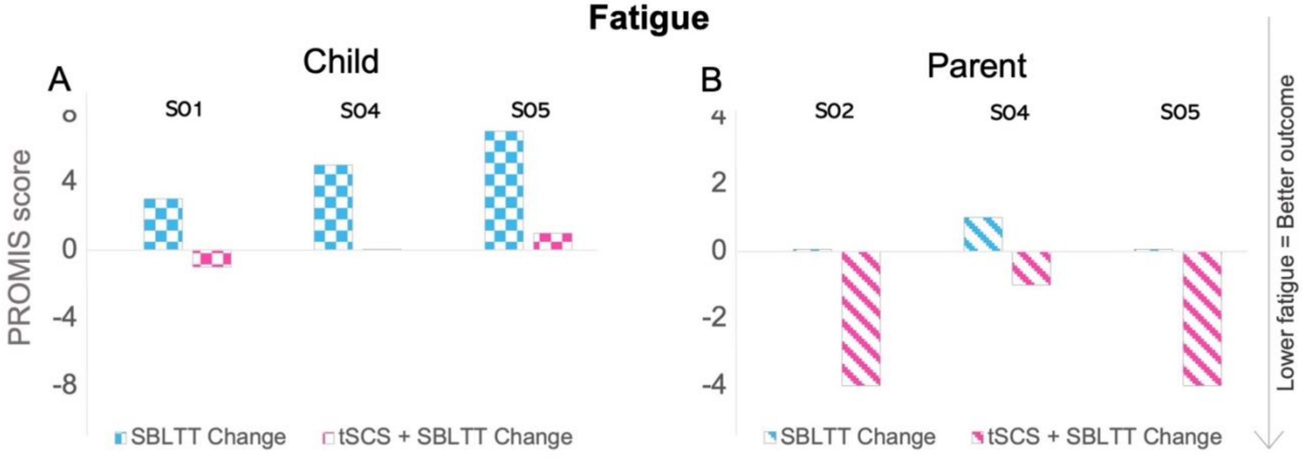


Figure 9. PROMIS Pediatric Profile – Fatigue shortform self-reported scores are presented, as reported by children (A) and parents (B).

3.4 Discussion

This study evaluated the effects of transcutaneous spinal cord stimulation (tSCS) and short burst interval locomotor treadmill training (SBLTT) across the ICF domains of Body Structure and Function, Activity and Participation. We observed substantially greater improvements in spasticity following tSCS + SBLTT compared to SBLTT only. The observed reductions in spasticity were sustained for three-months after stopping the tSCS + SBLTT intervention. Further, we found that walking function was maintained or continued to increase across interventions, despite marked improvements in spasticity. This is in contrast with most spasticity reducing treatments that weaken or paralyze a muscle, and often lead to reduced locomotor function (Butler et al., 2000; Chruscikowski et al., 2017; Multani et al., 2019; Munger et al., 2017; Pruszczynski et al., 2018; Vaughan et al., 1998).

Reductions in spasticity were sustained for three months after stopping tSCS. This is in contrast to oral baclofen that has a short half-life of 3-4 hours with poor blood-brain barrier penetration (Shellenberger et al., 1999), and similar to neurotoxin injections, such as botulinum toxin (Y. T. Chen et al., 2020). In addition, tSCS, does not have frequent side effects such as confusion, polyuria, headache, weakness, and orthostatic hypotension that come along with oral baclofen (Gough et al., 2007; Navarrete-Opazo et al., 2016).

Our results are different from that of a selective dorsal rhizotomy, which leads to permanent reduction in spasticity. Selective dorsal rhizotomy, however, is an irreversible procedure that also causes a reduction in sensory feedback and limits the ability of children in maintaining movement control (Wang et al., 2018). tSCS, on the other hand, may engage spinal network to enhance supraspinal-spinal connectivity in CP to form functional connections (Edgerton et al., 2021), as demonstrated by continued improvement in walking function throughout the current study.

Changes in walking function were clinically meaningful. All participants individually reached the minimal clinically important difference (MCID) for walking distances (Hassani et al., 2013) after both interventions, while the the youngest participant, surpassed the MCID by 3-fold. Time taken to complete the TUG reduced after both interventions. Lesser time on TUG indicates more functional mobility. Three out of four participant’s TUG times exceeded MCID after SBLTT only, and two out of four participant’s scores exceeded the MCID after tSCS + SBLTT (Carey et al., 2016a; Hassani et al., 2013).

Changes in walking distances, speeds and functional mobility were sustained for 3-months after discontinuing the stimulation. This indicates that SBLTT, alone and in combination with tSCS, durably improve walking distance, speeds and functional mobility. Taken together, spasticity and walking function results indicate that the combination of tSCS and SBLTT may also improve coordination, dynamic balance, motor planning and complex motor behavior. Future studies could include measures such as the Pediatric Evaluation of Disability Index (PEDI) or the Movement Assessment Battery for Children (MABC) to provide a comprehensive picture of children's abilities and limitations in performing complex motor tasks.

Along with these lab-based measures of walking function, self-reports of gait outcomes measured by child and parent versions of the GOAL questionnaire also improved across the study. A change in GOAL score greater than 5 points is greater than noise or variability and can confidently be attributed to the treatment (Thomason et al., 2018). Two out of three children and one out of four parents reported an increase of >5-points in the total GOAL score after tSCS + SBLTT. We also observed an interesting trend of an increase in scores in Domain E: Gait Patterns and Appearance. This is an important finding because it reflects on the subjective experience of improved gait patterns and appearance from participants. Taken together, the improvements in walking function and GOAL self-reports confirm the consistent trends of increase in walking function and mobility with tSCS + SBLTT.

3.5 Limitations

There are several limitations of this pilot study. First, the order of treatments was not randomized; each participant received SBLTT only first, and then tSCS + SBLTT. This design, however, was chosen to assess additional benefits of tSCS after an equal period of SBLTT only. Second, this study included a small sample, which limits the generalizability of the results to other children with CP. The age range of participants in this study, however, extended from 4- to 13-years-old with a GMFCS level of I and II. We observed improvements in spasticity and walking function across all of these ages and levels of motor functions. Third, we did not include blinding for tSCS, so the knowledge of receiving a new treatment may have led to a placebo effect. Blinding in stimulation research is often difficult due to the sensation associated with the stimulation. The observed substantial reductions in spasticity, which are difficult to volitionally control, reinforce that tSCS + SBLTT in fact had a treatment effect beyond placebo.

3.6 Conclusion

This study demonstrates that transcutaneous spinal cord stimulation and short burst interval locomotor treadmill training substantially reduce spasticity while simultaneously improving lab-based and self-reported walking function in four children with spastic cerebral palsy. Transcutaneous spinal cord stimulation was well-tolerated in four children with spastic cerebral palsy. The effects of transcutaneous spinal stimulation and short burst interval treadmill training were most evident in the Body Structure and Function, and Activity domains of the ICF. Future research should include randomized treatment groups and a larger sample size. Research efforts should be directed towards quantifying mobility-related participation and community ambulation to understand the effects of neuromodulation and training on children’s daily life.

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3.8 Supplemental Tables

Supplemental Table 1

Measure & ID	***Pre-SBLTT mean***	***Post-SBLTT mean***	***Pre-tSCS + SBLTT mean***	***Post-tSCS + SBLTT mean***	***Δ SBLTT only***	***Δ tSCS + SBLTT***
<u>1-MWT (m)*</u>						
S01	49.67	62.00	55.67	64.00	12.33	8.33
S02	61.98	69.24	60.42	79.28	*7.26*	18.86
S04	73.80	89.27	88.50	91.23	15.47	*2.73*
S05	129.31	150.97	152.17	161.33	21.66	9.16
<u>Self-selected 10 MWT (m/s)</u>						
S01	0.87	0.94	1.03	1.10	0.07	0.07
S02	1.07	0.20	1.11	1.27	-0.87	0.16
S04	1.22	0.94	1.07	1.31	-0.28	0.24
S05	1.34	1.49	1.47	1.40	0.15	-0.07
<u>Fast 10 MWT (m/s)</u>						
S01	1.56	1.56	1.57	1.58	0	0.01
S02	1.31	1.28	1.25	1.36	-0.03	0.11
S04	1.42	1.50	1.69	1.69	0.08	0
S05	2.45	2.65	2.10	2.63	0.2	0.53
<u>TUG</u>						
S01	11.09	7.45	7.76	7.9	-3.64	0.14
S02	8.53	8.07	8.69	6.85	-0.46	-1.84
S04	8.66	7.59	7.74	7.62	*-1.07*	-0.12
S05	5.20	5.03	4.68	4.77	-0.17	0.09

1-MWT: one minute walk test; *S01's six-minute walking distance was normalized to one minute; 10 MWT: 10-meter walk test; TUG: timed up and go; SBLTT: short burst interval treadmill training; tSCS: transcutaneous spinal cord stimulation; Δ: change

Supplemental Table 1. Walking function test results for SBLTT only and tSCS + SBLTT for n = 4 participants. Δ indicates the difference between pre- and post-intervention values for each intervention. SBLTT: short burst interval treadmill training; tSCS: transcutaneous spinal cord stimulation

Supplemental Table 2

ID	***Pre-SBLTT Only***	***Post-SBLTT Only***	***Pre-tSCS + SBLTT***	***Post tSCS + SBLTT***	***Δ SBLTT only***	***Δ tSCS + SBLTT***
Domain A. Activities of daily living						

S01	89	95	70	96	6	26
S04	96	99	99	100	3	1
S05	100	100	100	100	0	0
Domain B. Gait function and mobility						
S01	85	88	85	85	3	0
S04	92	88	86	91	-4	5
S05	97	99	96	98	2	2
Domain C. Pain, discomfort and fatigue						
S01	94	82	83	84	-12	1
S04	86	55	78	53	-31	-25
S05	85	100	91	88	15	-3
Domain D. Physical Activities, sports and recreation						
S01	77	NA	NA	NA	NA	NA
S04	73	74	69	74	1	5
S05	83	87	NA	NA	4	NA
Domain E. Gait pattern and appearance						
S01	56	69	61	69	13	8
S04	72	81	47	69	9	22
S05	63	83	78	86	20	8
Domain F. Use of braces and mobility aids						
S01	63	63	50	63	0	13
S04	50	50	50	75	0	25
S05	50	100	25	50	50	25
Domain G. Body image and self-esteem						
S01	50	50	50	54	0	4
S04	54	46	46	38	-8	-8
S05	46	54	75	83	8	8

Note: S02 did not complete the GOAL-child questionnaire due to his younger age. NA: Not enough data to calculate the domain score; SBLTT: short burst interval treadmill training; tSCS: transcutaneous spinal cord stimulation; Δ: change.

Supplemental table 2. Gait outcomes assessment list (GOAL)-Child version scores before and after each intervention.

Supplemental Table 3.

ID	***Pre-SBLTT Only***	***Post-SBLTT Only***	***Pre-tSCS + SBLTT***	***Post tSCS + SBLTT***	***Δ SBLTT only***	***Δ tSCS + SBLTT***
Domain A. Activities of daily living						
S01	69	72	70	72	3	2
S02	85	88	86	91	3	5
S04	**89**	78	75	77	-11	1
S05	84	85	85	88	1	3
Domain B. Gait function and mobility						
S01	60	66	65	73	6	8
S02	83	84	83	85	1	2
S04	73	72	73	72	-1	-1
S05	75	76	79	80	1	1
Domain C. Pain, discomfort and fatigue						
S01	90	88	57	80	-2	23
S02	92	NA	92	NA	NA	NA
S04	92	94	94	98	2	4
S05	84	79	80	80	-5	0
Domain D. Physical Activities, sports and recreation						
S01	57	NA	NA	NA	NA	NA
S02	40	53	47	NA	13	NA
S04	44	44	50	52	0	2
S05	52	44	52	50	-8	-2

Domain E. Gait pattern and appearance						
S01	36	33	42	56	-3	14
S02	53	61	58	61	8	3
S04	53	56	53	58	3	5
S05	42	50	56	53	8	-3
Domain F. Use of braces and mobility aids						
S01	63	50	38	50	-13	12
S02	50	50	50	50	0	0
S04	50	50	50	50	0	0
S05	50	25	25	0	-25	-25
Domain G. Body image and self-esteem						
S01	54	46	46	42	-8	-4
S02	50	50	50	50	0	0
S04	67	54	63	67	-13	4
S05	29	25	29	33	-4	4

NA: Not enough data to calculate the domain score; SBLTT: short burst interval treadmill training; tSCS: transcutaneous spinal cord stimulation; Δ: change.

Supplemental table 3. Gait outcomes assessment list (GOAL)-Parent version scores before and after each intervention.

Supplemental Table 4.

PROMIS-Child version							PROMIS-Parent version						
ID	***Pre-SBLTT Only***	***Post-SBLTT***	***Pre-tSCS + SBLTT***	***Post-tSCS + SBLTT***	***Δ SBLTT only***	***Δ tSCS + SBLTT***	***ID***	***Pre-SBLTT Only***	***Post-SBLTT***	***Pre-tSCS + SBLTT***	***Post-tSCS + SBLTT***	***Δ SBLTT only***	***Δ tSCS + SBLTT***
Mobility													
S01	36	35	38	34	-1	-4	S02	31	33	34	34	2	0
S04	29	29	30	34	0	4	S04	30	27	30	31	-3	1
S05	39	39	34	39	0	5	S05	29	31	33	32	2	-1
Anxiety													
S01	16	16	18	13	0	-5	S02	10	10	8	8	0	0
S04	21	M	20	22	M	2	S04	18	18	22	19	0	-3
S05	32	26	15	14	-6	-1	S05	27	25	21	22	-2	1
Depressive Symptoms													
S01	11	19	12	11	8	-1	S02	8	8	8	8	0	0
S04	21	29	22	25	8	3	S04	23	22	23	21	-1	-2
S05	25	28	21	14	3	-7	S05	28	27	28	30	-1	2
Fatigue													
S01	14	17	15	14	3	-1	S02	12	12	16	12	0	-4
S04	17	22	22	22	5	0	S04	17	18	17	16	1	-1
S05	16	23	18	19	7	1	S05	20	20	20	16	0	-4
Peer relationships													
S01	28	22	28	26	-6	-2	S02	23	25	28	31	2	3

S04	18	16	15	18	-2	3	S04	31	33	29	31	2	2
S05	23	37	23	36	14	13	S05	16	16	20	19	0	-1
Pain interference													
S01	11	12	8	10	1	2	S02	11	8	10	14	-3	4
S04	20	19	17	20	-1	3	S04	8	8	16	9	0	-7
S05	11	8	12	9	-3	-3	S05	8	13	12	10	5	-2
Pain intensity													
S01	1	2	2	2	1	0	S02	2	2	2	3	0	1
S04	4	5	6	4	1	-2	S04	0	0	1	0	0	-1
S05	1	1	1	1	0	0	S05	1	1	1	2	0	1

Note: S02 did not complete the child version due to his younger age; S01's parent did not complete the parent version. M: missing; SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation

Supplemental table 4. PROMIS-Child and Parent version results with changes before and after each intervention.

Chapter 4. Monitoring Walking Performance after Short Burst Interval Treadmill Training and Spinal Neuromodulation in Ambulatory Children with Cerebral Palsy

4.1 Abstract

4.1.1. Purpose To explore changes in community walking after two interventions, short burst interval locomotor treadmill training (SBLTT only) and transcutaneous spinal cord stimulation combined with SBLTT (tSCS + SBLTT).

4.1.2 Method Walking performance in the community was quantified using a StepWatch before and after each intervention using the following six variables: (1) average strides per day, (2) percent time in minutes, and (3) number of strides intensities of low, moderate, and high stride rates, (4) percentage of total strides at low, medium, and high intensities, (5) average peak stride rate, and (6) activity index. Stride data from five days for each participant across all timepoints were included. A total of 7200 minutes of stride data were used for analysis for each participant per treatment timepoint.

4.1.3 Results Children walked at high intensities after both interventions, with more high intensity strides measured after tSCS + SBLTT. There was a trend toward both more minutes spent and a higher percentage of total strides at medium and high intensities after both interventions. Little to no change was observed in average strides per day, peak stride rate and activity index.

4.1.4. Conclusion: Both SBLTT only and tSCS + SBLTT led to improvements in community walking intensity. StepWatch data can be valuable for measuring walking performance after physical therapy interventions in ambulatory children with cerebral palsy.

4.2 Introduction

Cerebral Palsy (CP) is an umbrella diagnosis that describes a group of permanent disabilities resulting from brain injuries before the age of two years old. CP can affect movement, posture, and motor function throughout life (Rosenbaum, 2006). CP affects motor capacity that may limit children's physical activity (Keawutan et al., 2014). As a result, children with CP have difficulties participating in activities across home, school and in the wider community (Calley et al., 2012). Restricted mobility is viewed by parents as one of the key barriers to participation for their child with a physical disability (Welsh et al., 2006). Epidemiological data suggests that about 45% of children with CP are capable of independent ambulation (Yeargin-Allsopp et al., 2008). Another study, however, reports that approximately 40% of ambulatory children have limitations in walking, running, and playing (Boulet et al., 2009). This could be because walking in the context of one's day to day environment entails navigating various environmental barriers, which may depend on the individual.

According to the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2002), walking *activity* can be examined by both capacity and performance-based measures. Walking *capacity* refers to what is typically measured in the clinical or laboratory settings and represents what the child is capable of doing in a structured setting. Walking *performance* symbolizes how a child fundamentally maneuvers in the context of everyday life. Walking *performance* includes walking in various environments such as school, communities, outdoors, and home. Capturing community-based walking, or performance, is an ecological complement to the current clinical and lab-based measures of walking capacity (Bjornson, 2019). Real-world mobility is vital, especially in childhood, because it can impact children’s ability to participate in daily activities and interact with their environment. Being able to move around in the real world may help children develop gross motor skills, which can improve their overall physical health and reduce the risk of secondary conditions such as osteoporosis and respiratory problems.

To influence the real-world walking of children, it is important that rehabilitation interventions and measurement techniques target walking *performance* as a complement to lab-based measures of mobility. Community-based walking activity and patterns are often measured by spatiotemporal parameters such as strides taken per minute (Barreira et al., 2012). The StepWatch is a two-dimensional, ankle mounted motion-sensitive activity monitor that has high accuracy in quantifying continuous step-by-step activity among children (McDonald et al., 2005). StepWatch instrument is an objective measurement technique that can be calibrated individually for each child. Its accuracy can be checked against walking trial samples. It measures physical activity intensity by reflecting both minute to minute variations in stepping activity and a cumulative measure of steps over time. Prior studies have reported that the StepWatch has excellent step-counting accuracy for children (McDonald et al., 2005; Mitre et al., 2009).

Here we used StepWatch to explore changes in walking performance after two different interventions, short burst interval treadmill training (SBLTT only) and transcutaneous spinal cord stimulation combined with SBLTT (tSCS +SBLTT), over a period of 10-12 months. SBLTT is a specialized training regimen, based on children’s natural walking patterns, that incorporates short bursts of 30-seconds at slow to moderate and high speeds for a total of 30-minutes (Bjornson et al., 2011, 2019). SBLTT improves walking speed, endurance and walking performance (Bjornson et al., 2019). tSCS is a novel non-invasive neuromodulation technique that may facilitate normal brain and spinal cord connectivity in children with CP (Edgerton et al., 2021). tSCS is applied through skin-surface electrodes and has a special waveform that allows for higher intensities without causing pain or discomfort (Gerasimenko et al., 2015).

The combination of tSCS and task-specific exercises improves hand and leg function in people with spinal cord injury and cerebral palsy (Gad et al., 2021; Hastings et al., 2022; Inanici et al., 2021; Samejima et al., 2022; Solopova et al., 2017). Whether the combination of tSCS and task-specific exercises improves community walking performance remains unknown. This is the first study to explore and compare the effects of the combination of the two interventions on real-world walking performance outcomes for children with CP. We tested the hypothesis that tSCS + SBLTT leads to greater walking performance in the community compared to SBLTT only.

4.3 Methods

4.3.1 Study Design and Participants

Participant received 24 treatment sessions each of SBLTT only followed by tSCS + SBLTT in a cross over design (Figure 1). We included a an 8-week washout period. between the two interventions to control for carryover effects of SBLTT only. The 24 intervention sessions in each intervention arm were distributed over 8-12 weeks, depending on participants’ availability. Data collection was conducted before and after each intervention, preSBLTT and postSBLTT for

SBLTT only and pretSCS and posttSCS for tSCS + SBLTT. Figure 1 represents the study timeline along with intervention phases and data collection timepoints.

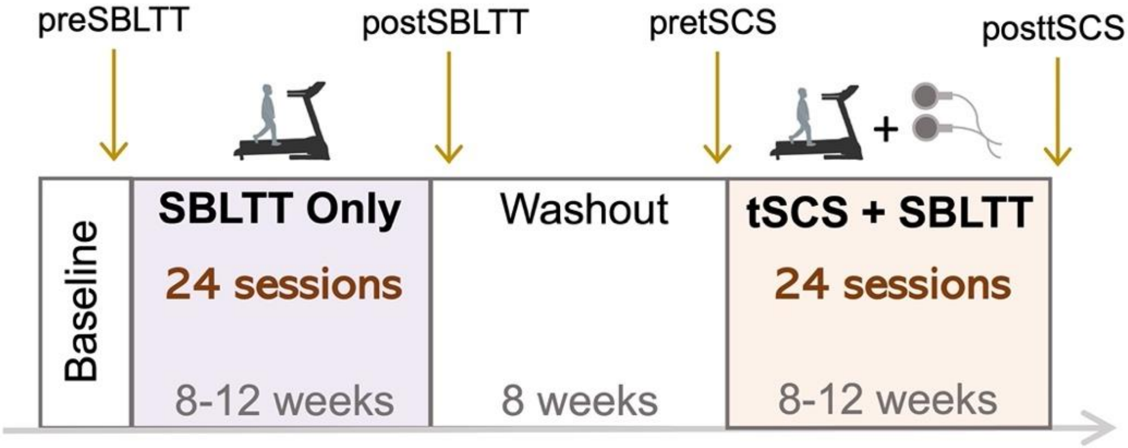

Figure 1. Study timeline and StepWatch data collection timepoints. To explore walking performance before and after SBLTT only, we compared preSBLTT and postSBLTT timepoints. To explore walking performance before and after tSCS + SBLTT, we compared pretSCS and posttSCS timepoints. SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

The inclusion criteria were as follows: (1) diagnosis of spastic cerebral palsy, (2) 4 to 17 years of age and (3) ambulatory with or without assistive devices. Exclusion criteria included: (1) uncontrolled seizures, (2) lower extremity surgery or spasticity medications in the last 6 months, (3) selective dorsal rhizotomy, and (4) metal implants such as cardiac pacemakers that would interfere with the tSCS. We collected demographic information and GMFCS levels by interviewing the parent and observing motor skills during a research consent visit.

4.3.2 Procedures and Outcomes

During a lab-based study visit at the University of Washington, participants were instructed to wear the StepWatch device on the lateral aspect of their left ankle for seven consecutive days during all waking hours except when showering, bathing or swimming. The overall goal was to capture 5 weekdays and 2 weekend days of walking activity. Participants were advised to wear the StepWatch device along with their current orthotics or assistive devices to obtain true representation of their real-world walking.

The StepWatch device is designed and validated for individualized calibration of walking stride patterns by considering height, stride type and activity level (Bjornson, et al., 2014; Puyau et al., 2002; Song et al., 2006). To calibrate the device to each individual, we conducted a walking trial of 100 steps and counted strides with a manual counter to compare with the StepWatch stride counts. Calibration was repeated at each timepoint. Calibration accuracy was verified to be between 95 to 105% for each participant at each data collection timepoint.

Dates that participants were instructed to wear the StepWatch device were recorded for analysis. Dates where <50 steps/day were recorded as non-compliant days, were filtered out, and eliminated from the final analyses. The first day of each timepoint was eliminated because this was the day that the device was initially donned and would therefore have incomplete data. The first weekend day was randomly chosen to be included in the analyses for consistency between timepoints and participants, unless that was the day the StepWatch device was donned. Data from 4 weekdays and 1 weekend day were included for the final analyses, as previously reported (Bjornson, Zhou, Stevenson, Christakis, et al., 2014). Walking activity intensity in no activity (0 strides/min), low stride rate (1–30 strides/min), moderate stride rate (31–60 strides/min) and high stride rate (>60 strides/min) (Bjornson, et al., 2014).

Walking performance was quantified using the following six variables: (1) average strides per day, (2) time (in minutes) and (3) number of strides intensities at low, moderate, and high stride rates, (4) percentage of total strides at low, medium, and high intensities, (5) average peak stride rate, and (6) activity index. Walking stride activity was derived from the average of five days of StepWatch data for each participant, as previously reported in the literature (Bjornson, et al., 2014).

4.3.3 Data Analysis

Data were stored and managed in Microsoft Excel (Microsoft Corporation. Microsoft Excel. 2018. Available from: https://office.microsoft.com/excel). All data processing, analysis and plotting were performed in R studio (2021.09.2 Build 382; RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

Average strides per day was calculated to explore whether the interventions led to an overall increase in the number of strides taken in the community. Average stride rates per day were calculated for each time point and individually compared for each participant. Time in minutes and average number of strides at low, medium, and high intensity were used to measure community walking intensity. Stride intensities were calculated by including raw stride counts per intensities at each timepoint. Average time spent in minutes and number of strides taken at each intensity at each timepoint were compared across interventions. Percentage of total strides at low, medium, and high intensities was calculated for each intensity by total steps taken at each timepoint.

Peak stride rate was used to compare whether the highest strides per minute were different between timepoints. To explore peak stride rate, we found the highest stride rate per day for each of the 5 days recorded. We then calculated the average stride rate per timepoint to compare between all data collection timepoints.

To explore whether the level of activity changed after interventions, we used the variable Activity Index. Activity Index was defined as the ratio of active minutes to inactive minutes. 24-hour data were filtered to only include awake minutes per day in the final analysis. Awake minutes for each day were calculated based on the first minute with non-zero strides and last minute with non-zero strides. This accounted for variability of sleeping patterns of children with different developmental ages. Activity minutes were defined as >0 strides/minute, while inactivity minutes were defined as 0 strides/minute. Data were sorted to separate activity minutes from inactivity minutes. We conducted repeated measure ANOVAs to evaluate whether the amount of inactivity was significantly different between timepoints.

Statistical analyses were conducted on combined data from all participants to test whether the average stride rates, peak stride rates and activity minutes from the activity index were significantly different between timepoints. First, Shapiro-Wilk normality tests evaluated the distribution of the data. For data that were normally distributed, repeated measure ANOVAs were conducted. For data that we not normally distributed, Kruskal Wallis tests were performed.

4.4 Results

Five participants consented to participate in the study. One participant, S03, withdrew from the study due to personal reasons prior to SBLTT only intervention. Four ambulatory children with spastic diplegia completed 24 sessions of SBLTT only and 24 sessions of tSCS + SBLTT. Data from these four participants are included for the exploratory analyses. Their demographics are listed in Table 1.

ID	***Age (years)***	***Gender***	***Diagnosis***	***Assistive/Mobility Device***
S01	12	Male	Spastic diplegia	Bilateral AFO-FC
S02	4	Male	Spastic diplegia	Bilateral AFO-FC
S04	10	Male	Spastic diplegia	Bilateral AFO-FC
S05	13	Male	Spastic diplegia	Shoe insert on left side due to leg length discrepancy

Table 1. Demographic and clinical characteristics of participants. AFO-FC: Ankle foot orthosis footwear combination.

StepWatch data with one-minute resolution was analzyed across 7200 minutes per timepoint for a total of 36000 minutes per participant. Walking performance was quantified using the following six variables: (1) average strides per day, (2) percent time, (3) number of strides, and (4) percentage of total strides intensities at low, moderate, and high stride rates, (5) peak stride rate, and (6) activity index. StepWatch activity was compared between pre-SBLTT and post-

SBLTT timepoints to explore treatment effects of the SBLTT only intervention arm, and between pre-tSCS and post-tSCS to explore effects of tSCS + SBLTT.

We observed a trend of increase in minutes spent at high intensity after both interventions SBLTT only, and tSCS + SBLTT (Figure 2). Specifically, the participants spent 1.5 times more minutes in high intensity walking after SBLTT only, and 27.78% more minutes after tSCS + SBLTT. Minutes and low and medium intensity reduced after SBLTT only (-2%, -23%) and tSCS + SBLTT (-6%, -12%) respectively. These changes in minutes, however, were not statistically significant for minutes spent at low (F(3, 76) = 0.12, p = 0.950; Eta2 = 4.57e-03, 95% CI [0.00, 1.00]), medium (F(3, 73) = 1.21, p = 0.312; Eta2 = 0.05, 95% CI [0.00, 1.00]) and high (F(3, 34) = 0.76, p = 0.522; Eta2 = 0.06, 95% CI [0.00, 1.00]) intensities. Average minutes spent at low, medium and high intensities, and percent change after each intervention are presented in supplemental table 1.

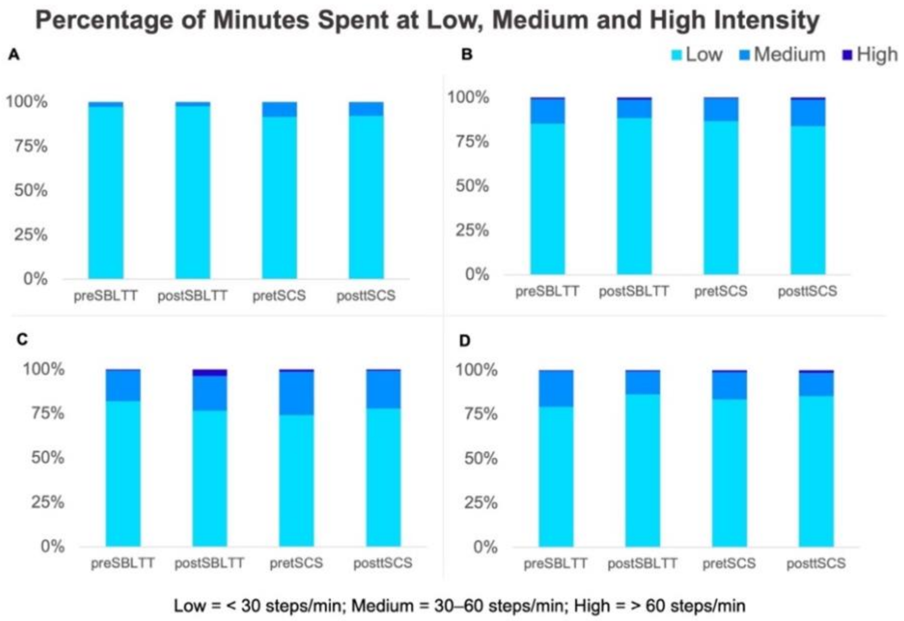

Figure 2. Percentage of minutes spent at low, medium and high intensities are presented for S01 (A), S02 (B), S04 (C) and S05 (D). Darker shades of blue indicate minutes at medium and high intensity strides.

Raw stride rates at low, medium and high intensities at each timepoint are presented in Figure 3. Number of high intensity strides improved after both interventions. All participants combined, 10-fold increase in high intensity strides was observed after SBLTT only, and 21% increase after tSCS + SBLTT. Number of low intensity strides were significantly different between timepoints (F(3, 11656) = 3.10, p = 0.026; Eta2 = 7.96e-04, 95% CI [5.12e-05, 1.00]). Bonferroni post hoc revealed that the low intensity strides were significantly different between preSBLTT and posttSCS timepoints (p=0.04), whereas pretSCS and posttSCS trended towards significance (0.06). Number of medium intensity strides were significantly different between timepoints (F(3, 2515) = 3.86, p = 0.009; Eta2 = 4.59e-03, 95% CI [6.54e-04, 1.00]). Post hoc revealed that medium intensity strides were significantly different between preSBLTT and pretSCS timepoints. Medium intensity strides at pretSCS and posttSCS timepoints trended towards significance (p = 0.09). High intensity strides were significantly different between time points (F(3, 161) = 3.34, p = 0.021; Eta2 = 0.06, 95% CI [5.06e-03, 1.00]). Post hocs revealed that high intensity strides were significantly different between preSBLTT and posttSCS timepoints (p = 0.045).

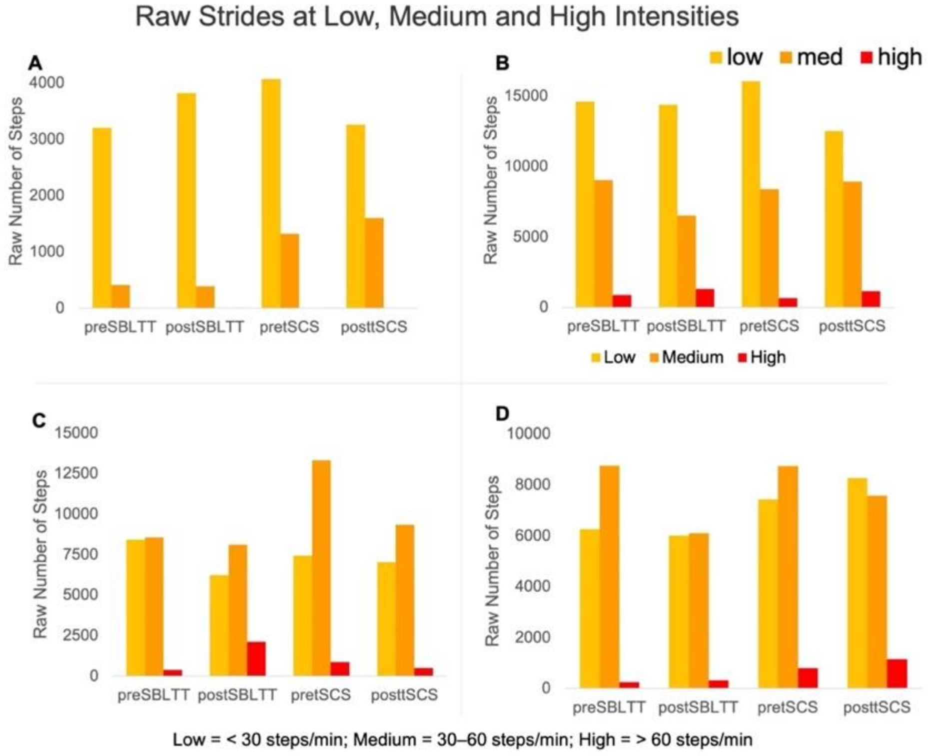

Figure 3. Raw stride rates taken at low, medium and high intensities at each timepoint for S01 (A), S02 (B), S04 (C) and S05 (D). Yellow, orange and red indicate stride rate of low, medium, and high intensity respectively.

In addition to average stride rates at low, medium, and high intensities, we also explored the percentage of total steps spent at each intensity (Figure 4). Percentage of total steps spent at low intensity increased by 1.5% after SBLTT only and 0.05% after tSCS + SBLTT. Percentage of total steps spent at medium intensity reduced by 5.9% after SBLTT only and by 1.3% after tSCS

+ SBLTT. Percentage of total steps spent at high intensity improved by 4.3% after SBLTT only and by 1.2% after tSCS + SBLTT.

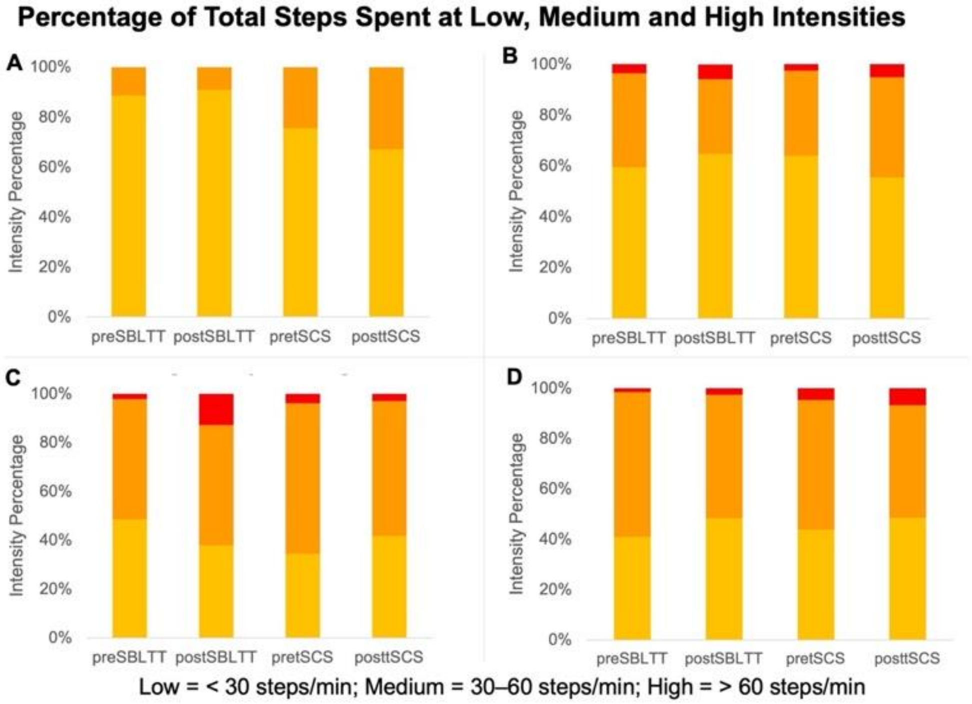

Figure 4. Percentage of total steps spent in low, medium and high intensities per timepoint.

Combined average stride rates were not significantly different between timepoints (F(3, 76) = 0.51, p = 0.676; Eta2 = 0.02, 95% CI [0.00, 1.00]). Little improvements were observed for individual participants. For example, average stride rates increased for S01 by 16.36% after SBLTT only and 0.07% after tSCS + SBLTT for S05 (Figure 5). Average strides per day and percentage change after each intervention for each participant individually are presented in supplemental table 2.

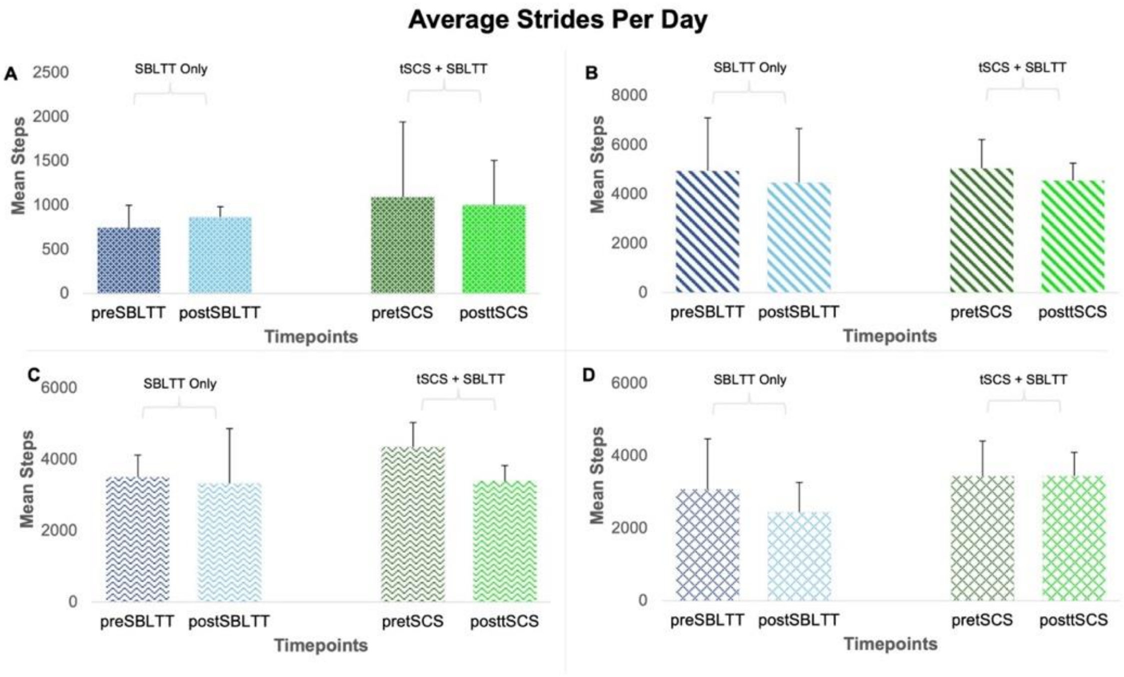

Figure 5. Average strides per day and standard deviations for each timepoint are reported for four timepoints: preSBLTT, postSBLTT, pretSCS and posttSCS. Average strides reduced for three out of four participants after SBLTT only and tSCS + SBLTT, except for S01 after SBLTT only and for S05 after tSCS + SBLTT.

There was a visible trend of increase in average peak stride rates in two out of four participants, S02 and S05, after tSCS + SBLTT (Figure 6), Over all, the combined average peak stride rate from four participants reduced by 0.8 +/- 0.57 strides/minute (1.5%) after SBLTT only and increased by 2.95 +/- 2.09 strides/minute (5.40%) after tSCS + SBLTT, but was not significantly different between time points (chi-squared = 1.31, df = 3, p = 0.73). Total and average stride rates per time point, and percent change after interventions for each participant are described in supplemental table 3.

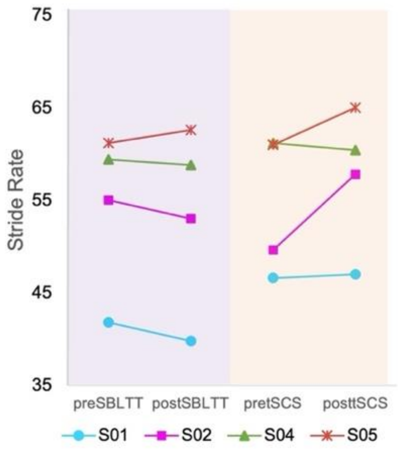

Figure 6. Average peak strides per time point are presented for S01 (blue), S02 (pink), S04 (green) and S05 (red).

No changes were observed in activity index, which was calculated by average active minutes/average awake minutes, for both interventions (Figure 7). Average active minutes were not significantly different between SBLTT and tSCS + SBLTT. (F(3, 12) = 0.05, p = 0.983; Eta2 = 0.01, 95% CI [0.00, 1.00]). Average awake, active and inactive minutes, and the activity index per participant are presented in supplemental table 4.

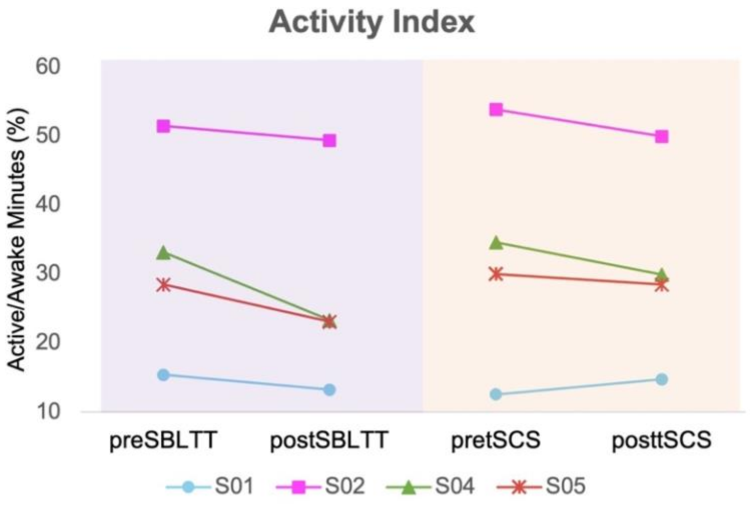

Figure 7. Activity index calculated by average active minutes/average awake minutes per timepoint. Little to no changes observed in activity index after both interventions.

4.5 Discussion

This study demonstrates the utility of the StepWatch device to measure walking performance after two interventions: short burst interval locomotor training (SBLTT) and transcutaneous spinal cord stimulation combined with SBLTT (tSCS + SBLTT) in four ambulatory children with CP. Ambulatory children with CP take significantly fewer steps per day and spend less time in high intensity walking in the community as compared to their typically developing peers (Bjornson et al., 2007; Bjornson, Zhou, Stevenson, Christakis, et al., 2014). Walking activity greater than 30 strides/min has documented association to mobility-based participation in ambulatory children with CP (Bjornson, 2014).

In this study, we observed a trend of more strides at medium and high walking intensities after both interventions, indicating that children did more intense walking after the interventions. More high intensity strides were observed after tSCS + SBLTT, highlighting that tSCS + SBLTT may have an added benefit on walking performance over SBLTT alone. These results are similar to prior SBLTT studies in which the participants walked at more medium and high intensity stride rates after SBLTT intervention (Bjornson et al., 2019).

There was a trend of increase in minutes spent at medium and high intensities after both interventions. More minutes were also spent at high intensity stride after SBLTT only and tSCS + SBLTT as compared to before the interventions. This is an important finding because high intensity strides have positive associations with walking endurance and gross motor function (Wittry et al., 2018).

The average number of strides per day and activity index did not change after either intervention. Average number of strides per day is dependent on many external factors such as school schedules, family dynamics, etc. Therefore, it is possible that an intervention may not have a direct influence on the number of strides children take per day. This could also be because of the longitudinal nature of the study, wherein the amount of walking activity and awake minutes could depend on seasonal variations and school schedules. Future studies should evaluate the effects of gait training and stimulation interventions on these variables in a larger sample of ambulatory children with CP.

Taken together, the results suggests that the children walked at higher intensities but were not necessarily walking more after SBLTT and tSCS + SBLTT. Further, each intervention had similar effects on improved walking intensity.

4.6 Limitations

The results of this exploratory study must be interpreted in the context of known limitations. First, this study included a small sample size. This limited the statistical procedures that could be applied to the data to test for significant results. Despite a small sample size, however, the age ranges of participants extended from 4 to 13 years old and included two GMFCS levels of disability. Future studies should include a larger sample size to provide a better representation of the population and increased generalizability of results. Second, during home use of the StepWatch, were unable to precisely control the exact device measuring duration across the child's typical activity patterns. Nonetheless, StepWatch is a well-validated device, and children were instructed to wear the device all day except showering, swimming and bedtime. To further mitigate variation in device wearing, we included data from first non-zero minute to last non-zero minute of each recorded day.

4.7 Conclusion

Walking intensity, measured by strides and minutes at low, medium and high intensities improved after both interventions, SBLTT only and tSCS + SBLTT. Little to no change were observed in average strides per day, peak stride rate and activity index. Overall, StepWatch can be a valuable tool to measure walking performance after physical therapy interventions in ambulatory children with cerebral palsy.

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4.9 Supplemental Tables

Supplemental Table 1.

ID	*Intensity*	*preSBLTT (mins)*	*postSBLTT (mins)*	*pretSCS (mins)*	*posttSCS (mins)*	*% SBLTT change*	*% tSCS + SBLTT change*
S01	Low	421	448	396	462	6.41%	16.67%
S01	Medium	12	11	36	39	-8.33%	8.33%
S01	High	0	0	0	0	0.00%	0.00%
S02	Low	1407	1417	1504	1223	0.71%	-18.68%
S02	Medium	230	166	221	219	-27.83%	-0.90%
S02	High	14	21	10	18	50.00%	80.00%
S04	Low	941	705	847	775	-25.08%	-8.50%
S04	Medium	202	182	281	214	-9.90%	-23.84%
S04	High	6	34	14	8	466.67%	-42.86%
S05	Low	776	906	1049	1105	16.75%	5.34%
S05	Medium	199	139	196	172	-30.15%	-12.24%
S05	High	4	5	13	18	25.00%	38.46%

Supplemental Table 1. Average minutes spent at low, medium and high intensities, and percent change after each intervention. SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

Supplemental table 2.

ID	*preSBLTT*	*postSBLTT*	*pretSCS*	*posttSCS*	*SBLTT change*	*tSCS change*
S01	743.2	864.8	1091.2	1002.4	16.36%	-8.14%
S02	4938.8	4474.8	5052.8	4543	-9.39%	-10.09%
S04	3509	3323	4350	3390	-5.30%	-22.07%
S05	3080.4	2531	3441	3443	-17.82%	0.07%

Supplemental Table 2. Average strides per day and percentage change after each intervention. SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

Supplemental Table 3.

ID	***preSBLTT***	***postSBLTT***	***pretSCS***	***posttSCS***	***SBLTT only***	***tSCS + SBLTT***
	Total (mean)				% change	
S01	209 (41.8)	199 (39.8)	233 (46.6)	235 (47)	-4.78%	0.86%
S02	275 (55)	265 (53)	248 (49.6)	289 (57.8)	-3.64%	16.53%
S04	297 (59.4)	294 (58.8)	306 (61.2)	302 (60.4)	-1.01%	-1.31%
S05	306 (61.2)	313 (62.6)	305 (61)	325 (65)	2.29%	6.56%

Supplemental table 3. Total and mean peak stride rates across timepoints. Percentage change for SBLTT only and tSCS + SBLTT is also included. SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

Supplemental Table 4.

ID	***Timepoint***	***Average awake minutes***	***Average active minutes***	***Average inactive minutes***	***Activity Index***
S01	preSBLTT	560.60	86.60	474.00	15.45
S01	postSBLTT	691.40	91.80	599.60	13.28
S01	pretSCS	689.60	86.40	603.20	12.53
S01	posttSCS	678.20	100.20	578.00	14.77
S02	preSBLTT	641.20	330.20	311.00	51.50
S02	postSBLTT	649.00	320.80	328.20	49.43
S02	pretSCS	644.20	347.00	297.20	53.87
S02	posttSCS	584.20	292.00	292.20	49.98
S04	preSBLTT	693.00	229.80	463.20	33.16
S04	postSBLTT	790.40	184.20	606.20	23.30
S04	pretSCS	660.00	228.40	431.60	34.61
S04	posttSCS	665.60	199.40	466.20	29.96
S05	preSBLTT	687.40	195.80	491.60	28.48
S05	postSBLTT	908.40	210.00	698.40	23.12
S05	pretSCS	839.20	251.60	587.60	29.98
S05	posttSCS	908.60	259.00	649.60	28.51

Supplemental table 4. Average awake, active and inactive minutes. Activity index calculated by average active minutes/average awake minutes is presented. SBLTT: short burst interval locomotor treadmill training; tSCS: transcutaneous spinal cord stimulation.

Chapter 5. Discussion and Conclusion

5.1 Summary of Main Findings

The work presented in this dissertation focuses on improving spasticity, walking function and walking performance in children with cerebral palsy (CP). Children with CP experience spasticity, which negatively affects their walking function. Current spasticity management techniques are invasive, permanent and may negatively affect sensory feedback that is critical during development. The aim of this research was to determine the effects of transcutaneous spinal cord stimulation (tSCS) and short burst interval locomotor treadmill training (SBLTT) in children with spastic CP. tSCS is a novel non-invasive neuromodulation technique that utilizes a high-frequency waveform that can enable higher amplitudes without causing discomfort. This increases its value in pediatric rehabilitation. SBLTT is a specialized treadmill training that is based on children's natural walking patterns. We aimed to understand whether the combination of tSCS and SBLTT has additional benefits over SBLTT alone. Our findings suggest that both SBLTT only and tSCS combined with SBLTT improve walking function. The combination of tSCS and SBLTT, however, significantly reduces spasticity as compared to SBLTT alone. Moreover, reductions in spasticity sustain over at least 3-months after stopping all interventions. Children with spastic CP may benefit from the combination of tSCS and SBLTT. Our discovery of long-lasting reductions in spasticity highlights that the combination of tSCS and SBLTT could be a valuable spasticity management tool in this population.

In Chapter 2, findings from a case study are presented. A prospective crossover of two interventions with a washout period in between was delivered to two ambulatory children with

CP. The combination of tSCS and SBLTT resulted in considerable reductions in spasticity. Walking distance, speed and mobility improved after both interventions, SBLTT only and tSCS combined with SBLTT. This case study provided preliminary evidence that spinal cord neuromodulation can reduce immediate and long-term spasticity, while promoting functional gains in ambulatory children with CP.

In Chapter 3, findings from a larger case study are presented. Four ambulatory children with CP completed a cross-over program of two interventions, SBLTT only and tSCS combined with SBLTT. In this 12-month longitudinal study, participants received 24 sessions of SBLTT only, followed by an 8-week washout period. Participants then received 24 sessions of the combination of tSCS and SBLTT. Spasticity, measured by two clinical measures, improved considerably after the combination tSCS and SBLTT compared to SBLTT alone. Walking function and mobility improved after both interventions. Self-reported gait outcomes, captured through child and parent self-reported questionnaires, improved after both interventions, with greater scores after the combination of tSCS and SBLTT. Parent-reported fatigue measures revealed that fatigue reduced substantially with the combination of tSCS and SBLTT. Improvements in spasticity and walking function were sustained for at least 3-months after stopping tSCS. These findings suggest that the combination of tSCS and SBLTT may reduce spasticity, improve walking function and may also have an impact on patient perceptions of gait and fatigue.

In Chapter 4, findings from community walking, also known as walking performance, are discussed. This chapter explores trends in walking performance variables after two interventions, SBLTT and tSCS combined with SBLTT. Walking performance in the community was quantified using a StepWatch that was worn on left ankle before and after each intervention. The number of strides and minutes walking at high intensities improved after both interventions, SBLTT only and tSCS + SBLTT. Little to no change was observed in average strides per day, peak stride rate and activity ratio. Overall, this study highlights that StepWatch can be a valuable tool to measure walking performance after physical therapy interventions.

Overall, findings presented in this dissertation suggest that the combination of tSCS and SBLTT could be a valuable spasticity reduction tool. tSCS utilizes a high-frequency waveform that can enable higher amplitudes without causing discomfort, which increases its value in pediatric rehabilitation. Along with spasticity, the combination of tSCS and SBLTT can improve walking function and walking intensity in the community.

5.2 Contributions

This is the first study to evaluate whether the combination of spinal neuromodulation and intensive treadmill training leads to more functional improvements than intensive treadmill training alone. The findings indicate that spinal neuromodulation (tSCS) and SBLTT lead to significantly less spasticity than SBLTT alone. The combination of tSCS and SBLTT simultaneously improves walking function. The resulting improvements in both spasticity and walking function exceed the common standard of care surgery, selective dorsal rhizotomy, which negatively affects mobility.

This is the first study to report on the long-term effects of the combination of spinal neuromodulation and treadmill training. The discovery that the reductions in spasticity and improvements in walking function are sustained for 3-months provide evidence of neuroplasticity promoted by the combination of tSCS and SBLTT.

Improvements in walking function, importantly, were also perceived by children and parents and were reported in the Gait Outcomes Assessment List (GOAL) questionnaire. Considerable reduction in fatigue was also reported by parents with the combination of tSCS and SBLTT. These findings suggest that tSCS and SBLTT can positively impact important aspects of mobility.

Both SBLTT and the combination of tSCS and SBLTT improved walking intensity aspect of walking performance in the community. This indicates that both interventions have a positive impact on children's day-to-day mobility and may contribute towards mobility-based participation.

Overall, this research provides preliminary evidence that the combination of transcutaneous spinal cord stimulation and short burst interval treadmill training is a promising intervention for ambulatory children with spastic cerebral palsy. This combinatorial treament has an advantage over the selective dorsal rhizotomy surgery, in that it is non-invasive, well tolerated by children, and does not negatively affect sensory feedback.

5.3 Future Directions

The work presented in this dissertation opens new questions for future research. Understanding mechanisms by which transcutaneous spinal cord stimulation drives functional gains will facilitate our understanding of the optimal parameters, location and duration of stimulation. This will in turn improve the beneficial effects of transcutaneous spinal cord stimulation when combined with task-specific training.

While this research was limited by its small sample size, future studies are needed to improve the generalizability of the findings. Randomized controlled trials with assessor blinding would be beneficial to evaluate cause-effect relationship between the interventions and functional changes and reduce bias.

The work presented here provides preliminary evidence on the effectiveness of transcutaneous spinal cord stimulation and short burst interval treadmill training in 4–13-year-old ambulatory children with spastic cerebral palsy. Future work should be tailored to understand which subset of the cerebral palsy population could benefit the most from the combination of transcutaneous spinal cord stimulation and short burst interval treadmill training.