COMPENSATORY STEPPING THRESHOLDS IN CHILDREN WITH AND WITHOUT CEREBRAL PALSY

by

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ABSTRACT

Cerebral palsy (CP) is a non-progressive neurological disorder that arises from injury, typically at infancy, to the brain, resulting in permanent effects on muscle coordination, movement, and balance. These impairments to movement and balance likely underly the high incidence of falls reported for adults with CP. Investigations of the effects of CP on balance have been primarily limited to quasi-static measures of postural sway and functional assessments, both of which are limited as predictors of falls in the free-living environment. The ability to arrest a fall in response to external balance perturbations has been shown to be prospectively related to falls in older adults. We can quantify this fall-recovery ability with single-stepping thresholds, or the disturbance magnitudes that consistently elicit anterior and posterior compensatory steps. To date, the effects of CP on the fall-recovery response have been inconclusive. The purpose of this study was to 1) determine whether children with CP have an impaired ability to respond to external postural disturbances, as evident by lower stepping thresholds, and 2) determine whether children with CP have altered neuromuscular responses and dynamic stability maintenance after an external postural disturbance.

Three children with spastic CP between the ages of five and twelve, and gross motor function classification I – II, participated in the study. Fourteen typically developing children in the same age range also participated. Participants attempted to

prevent steps in response to a progressive series of rapid, precise treadmill belt accelerations delivered by a computer-controlled treadmill. Each participant's anterior and posterior single-stepping thresholds were determined, as represented by the disturbance magnitudes that consistently elicited a step in each direction. The neuromuscular response about the ankle was assessed, and the resulting dynamic stability was quantified in an attempt to identify underlying mechanisms of anticipated group differences. These mechanisms were assessed for the successful, non-stepping trials at disturbance magnitudes immediately below threshold values.

Children with CP had significantly lower single-stepping thresholds in both the anterior (Cohen's d (d) = 2.579, p = 0.003) and posterior (d = 1.556, p = 0.047) directions. These differences were associated with moderate to large differences in the minimum margin of stability for the anterior (d = 0.808, p = 0.300) and posterior (d = 1.049, p = 0.032) direction, indicating a greater ability to recover from dynamic instability without a step in children with typical development. Analyses of the neuromuscular response revealed longer muscle onset latencies for both the medial gastrocnemius (dominant: d = 2.565, p = 0.033; non-dominant: d = 2.188, p = 0.019) and tibialis anterior (dominant: d = 2.528, p = 0.033; non-dominant: d = 2.018, p = 0.033) when their role was the agonist muscle. In addition, the activation amplitude of the tibialis anterior as an agonist was lower in children with CP than controls (dominant: d = 1.596, p = 0.067; non-dominant: d = 1.763, p = 0.017). The results from this study indicate that children with CP have a compromised fall-recovery, as represented by the ability to prevent a step in response to external balance

perturbations. These differences may be due to a delayed, insufficient neuromuscular response and an inability or unwillingness to recover from dynamic instability.

Chapter 1

INTRODUCTION

1.1 Overview

Cerebral palsy (CP) is a non-progressive neurological disorder resulting from injury to the brain before cerebral development is complete. It is one of the most common causes of physical disability in children, and it leads to impairment in motor control that limits mobility [1] and impairs postural control [2]. Adults with CP exhibit a high incidence of falling and fall-related injury, as well as a high prevalence of fear of falling [3, 4]. Although not documented in the literature, children with CP likely have a similarly high risk of falling, injury, and fall-related fear. These aspects serve as barriers to physical activity. The risk of falling is, therefore, a target for interventions to reduce injury and enable physical activity.

One aspect of postural control that influences fall risk is the ability to recover from a fall. Although the neuromuscular response to postural disturbances appears to be altered with CP [5, 6], the effects of CP on the *ability* to recover from a fall have not been quantified. An assessment that has been prospectively related to falls in older adults is the ability to prevent or minimize the number of steps after a perturbation [7, 8]. Single-stepping thresholds, or the perturbation magnitudes that consistently elicit an anterior or posterior step, objectively and reliably quantify fall-recovery ability [9]. To date, this assessment has not been applied to children with CP. By quantifying the deficits in fall-recovery ability associated with CP using stepping thresholds, in conjunction with biomechanical analyses of resulting dynamic stability and the

neuromuscular response to the perturbation, we will identify new targets for interventions to reduce falls and enable physical activity in this population.

1.2 Significance

As a long-term chronic disability, CP requires a lifetime of rehabilitation services, resulting in an average lifetime cost per person of nearly $1 million dollars. This leads to an estimated $11.5 billion dollars total in lifetime costs [1]. Falls are likely a direct and indirect determinant of these costs, with 97% of adults with CP falling annually [4]. In addition, children with CP are susceptible to femur fractures due to an underdeveloped architecture, and nearly half of these fractures are due to a fall. Falls can lead to adverse interrelated outcomes, such as a fear of falling [4]. Fear of falling by both individuals with CP and their caretakers can lead to decreased levels of physical activity [3], which may explain the significantly lower levels of physical activity reported in children with CP relative to those with TD [10]. Decreased levels of physical activity lead to impaired motor function [11]. Furthermore, low levels of activity translates into relative unloading of the body, the negative effects of which can be seen in the significantly underdeveloped musculoskeletal system in children with CP [12 – 14]. In addition, the significantly lower levels of physical activity in children with CP may be contributing to the higher rates of chronic disease seen in adults with CP [15]. As a result, investigating fall risk and its potential underlying mechanisms in children with CP is paramount in addressing the low levels of physical activity and reducing the incidence of fractures and chronic disease in this population. The contribution of this study will be to quantify deficits in fall-recovery ability associated with CP in children. *This contribution is significant because it may reveal*

new targets for interventions to decrease fall risk and subsequently enable physical activity in this population.

1.3 Purpose

The purpose of this pilot study was to assess differences in the fall-recovery response between children with CP and children with typical development.

1.4 Hypothesis

It was hypothesized that children with CP would have an impaired response to balance perturbations, as characterized by lower anterior and posterior single-stepping thresholds.

1.5 Limitations

The candidate underlying mechanisms of dynamic stability and muscle activity may be assessed at different perturbation magnitudes across typically developing and CP groups. This disparity in magnitudes may influence the subsequent outcomes of stability and muscle activity. Our analysis is designed to assess the child's response when stability is threatened, necessitating a rapid, large, and coordinated muscular response. Therefore, we chose to analyze disturbance magnitudes relative to the child's capabilities. If the response to a common disturbance acceleration is compared across subjects, those individuals who are not challenged to prevent a step may demonstrate a delayed, small muscle response that was sufficient, but not characteristic of the individual's maximum capabilities. An additional limitation is that we are constraining the stepping response, when that constraint is rarely present in the

free-living environment. The stepping response may also be altered with CP in a way that increases fall risk. However, constraints were made to allow for a reliable measure that could be evaluated by observation alone, as opposed to recovery kinematics necessitating motion capture technology.

Chapter 2

LITERATURE REVIEW

2.1 Overview

Cerebral palsy (CP) is a movement disorder that leads to impairments in balance. Adults with CP have a high incidence of falls compared to healthy adults [4], a characteristic trait that likely begins in childhood. Falls can result in injury, such as fractures, particularly for children with CP who have an underdeveloped skeletal system [12 – 14]. In addition, falls can lead to adverse interrelated outcomes, such as fear of falling [4]. The high incidence of falls, fall-related injury, and a fear of falling likely contribute to the low physical activity levels for children with CP [10]. Low physical activity levels lead to decreases in motor function [11], which can further increase the risk of falls. Inactivity also leads to relative unloading of the skeleton that prevents the necessary mechanical input for ontogenesis with development. Ultimately, the direct and indirect effects of falls on physical activity levels can lead to increased risk of chronic disease for individuals with CP [15] (Figure 1). The proceeding text will review relevant literature on the etiology and epidemiology of CP, associated symptoms, postural control and falls, musculoskeletal development and fracture risk, and physical activity levels and chronic disease in this population. In addition, this review will cover current measures of fall-recovery ability, and interventions that could be applied to improve this ability in children with CP.

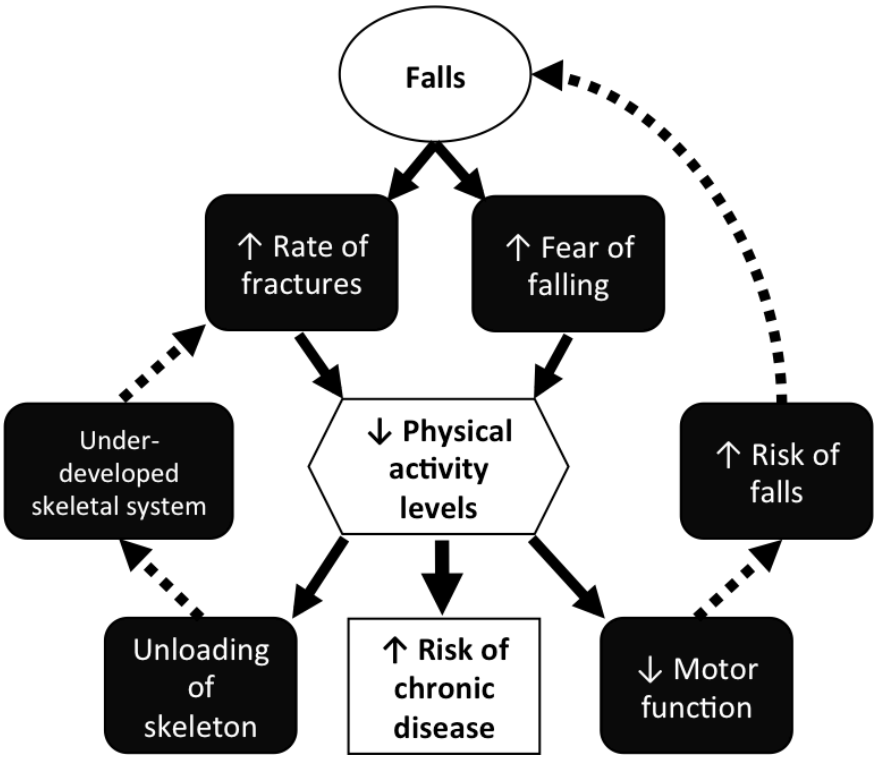

Figure 1. A model displaying the direct and indirect effects of falls in children with CP

2.2 Etiology and Epidemiology of Cerebral Palsy

CP results from injury to the brain before cerebral development is complete. Cerebral development occurs during the first two years of life, so the etiology of CP can arise from injury during prenatal, perinatal, or postnatal developmental periods. The majority of incidences occur during the prenatal period, with 70 – 80% of CP cases being acquired during this time due to largely unknown causes. Birth complications in the perinatal period, such as asphyxia, account for approximately 6% of cases. Additionally, neonatal risk factors such as premature births, low birth weight, intracranial hemorrhage, trauma, and intrauterine growth retardation can lead to CP. Finally, approximately 10 – 20% of cases occur with postnatal brain damage due to such incidences as bacterial meningitis, hyperbilirubinemia, viral encephalitis, falls,

child abuse, or motor vehicle accidents [16]. The common theme throughout, however, is some form of encephalopathy to the developing central nervous system (CNS).

2.3 Symptoms

The phenotype of CP is highly heterogeneous. Part of this heterogeneity is the variation in lesion magnitude, as well as the fact that CP can be acquired at different stages of development. The developing brain can be influenced by experience, and the capacity to do so is known as plasticity. On top of explaining the innate ability of children to learn and become proficient at complicated tasks, plasticity also gives children a remarkable ability to recover from early brain injuries [17]. The level of plasticity in the CNS will depend on where the child is in development, and this plasticity heavily dictates the ability of the child to recover from brain injury and acquire motor skills. As CP can be acquired at any point during the first two years of life, the brain's response to injury can differ significantly, leading to a large spectrum of disabilities associated with the disease. To assist clinicians with prescribing appropriate treatment plans and descriptively classifying level of motor function, a gross motor function classification system (GMFCS) that consists of five levels (Level I-V) was developed and validated for individuals with CP. Level I describes children who can ambulate independently and only have limitations with more advanced motor skills, while Level V describes children who have severely limited mobility even with assistive technology [18]. In addition, CP can be either spastic or non-spastic, and have several different topographical distributions. Affecting approximately 75% of individuals, spastic CP is the most common form of this neurological disorder [19],

and is characterized by increased and velocity-dependent muscle tone of the extremities on one or both sides.

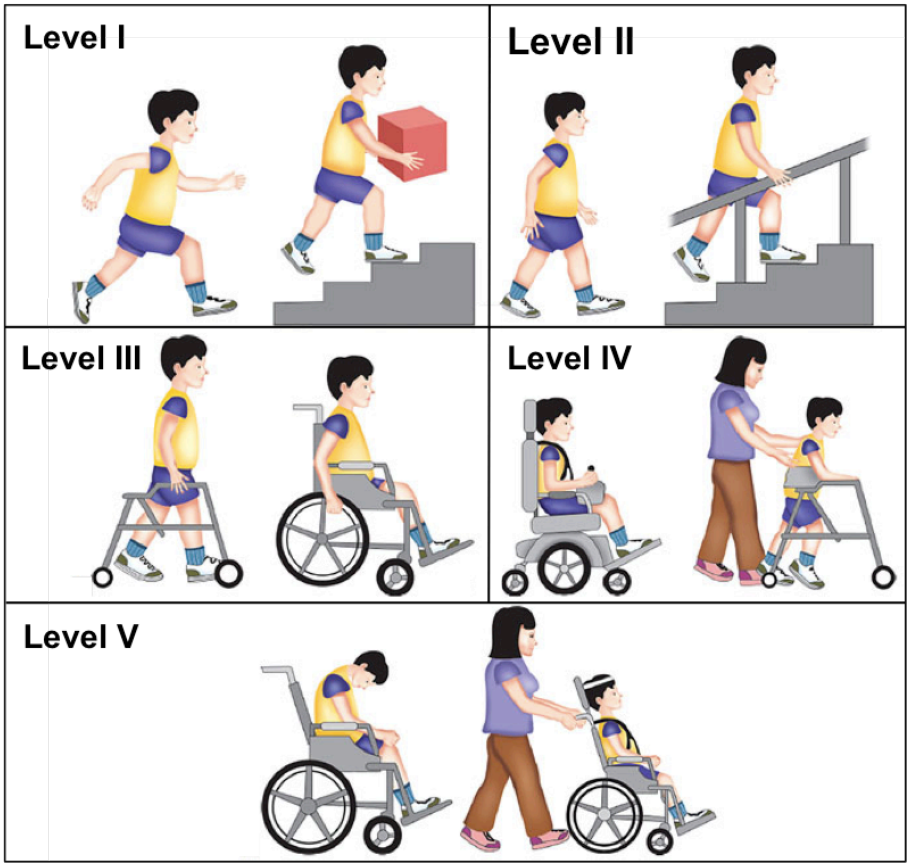

Figure 2. Gross motor function classification system (GMFCS) levels. Adapted from Sehrawat N et al 2014, *International Journal of Clinical Pediatric Dentistry*, *7*(2), 109 – 118.

Individuals with CP who experience spasticity have an imbalance between excitatory and inhibitory neural impulses. It is believed that this imbalance is due to a lack of inhibitory signals as a result of damage to descending tracts from the brain, leading to a relative excess of excitatory impulses and increased muscle tone [20].

This hypothesis is supported by the fact that spastic CP is linked to damage of the periventricular leukomalacia ring, which disrupts the corticospinal tracts [21]. Corticospinal projections of children with CP can branch abnormally in order to originate from the undamaged motor cortex [22, 23]. Changes to these descending tracts may hinder the arrival of inhibitory impulses, leading to hypertonia. Unfortunately, a muscle affected by spasticity for several years can develop permanent shortening due to fibrosis. At this stage, even if a muscle is relieved of its spastic quality, the muscle will remain shortened and can only be corrected with orthopedic operations [20].

A characteristic feature of neuromuscular control in children with CP is the presence of co-activation between agonist and antagonist muscle groups. Effective movements require activation of synergistic alpha motor neurons to contract specific muscle groups, along with inhibition of antagonist muscle groups that would oppose this movement. This coordination is achieved by dual signaling from muscle spindles to both homonymous alpha motor neurons of the target muscle and segmental inhibitory interneurons that inhibit the alpha motor neurons of antagonist muscles, a process known as Ia reciprocal inhibition. A similar process involving polysynaptic connections from Golgi tendon organs also takes place, and is known as nonreciprocal inhibition [24]. In children with CP, there appears to be a failure of one or both of these mechanisms. In addition, there is evidence that supraspinal centers are responsible for the simultaneous activation of antagonist muscle groups, whereby the reorganization of corticospinal projections has led to abnormal connectivity. Given the heterogeneity of CP, there are likely several unique and interdependent factors that contribute to the neuromuscular abnormalities experienced by an individual [25, 26].

2.4 Postural Control and Falls

The neuropathophysiology of spasticity and co-contraction in children with CP can affect the sensory inputs that govern postural control. Effective postural control relies on the integration of sensorimotor processes, including vision, vestibular, and proprioception [24]. It is likely that proprioception is negatively affected in this population due to the high prevalence of spasticity. Proprioception involves the input of mechanoreceptors in muscle and joints to sense the stationary position and movement of the limbs. Specifically, proprioception relies on signaling from muscle spindle receptors and Golgi tendon organs [24]. The common presentation of spastic muscle and co-activation with volitional movements in CP provides strong evidence that the processes necessary for muscle spindles and Golgi tendon organs to contribute to proprioception are compromised. For this reason, the ability to sense position and movement of one's own limbs and body becomes more difficult. While it has not been studied specifically in CP, spasticity has been shown to contribute to postural deficits in individuals with multiple sclerosis [27, 28]. Individuals with multiple sclerosis and high levels of spasticity have been shown to exhibit greater sway, particularly in the medial-lateral direction, during tasks of quiet standing compared to individuals with low spasticity and a control group. This difference in sway has been attributed to deficits in proprioception due to an inability to regulate normal ankle stiffness [27, 28]. In addition to this, the simultaneous activation of antagonist muscle groups [26] may be hindering the effective and direction-specific movements necessary for maintaining upright stance. A combination of these factors is likely part of the underlying mechanisms behind balance and postural control deficits in children with CP.

Standing sway can serve as an indicator of one's postural control abilities. In one study [29] postural sway in nine children with CP and nine age-matched, typically developing (TD) children were compared. Subjects were asked to stand as still as possible on a force plate under three conditions: standing upright with eyes open, standing upright with eyes closed, and standing upright with visual center of pressure (COP) feedback. Although not to the point of significance ($p = 0.062$), sway amplitude, or COP excursion, was higher in all conditions for children with CP, accompanied by a large effect size ($\eta^2_p = 0.10 – 0.46$). The TD group did have significantly greater entropy ($p < 0.001$), indicating a more regular sway for children with CP. This finding was connected to the 'pathological regularity versus healthy complexity' hypothesis, whereby a more regular COP pattern is indicative of less effective physiological control of posture. Conducting a similar experiment but with 23 children with CP, another study found that children with CP had significantly greater standing sway when compared to normative data from 92 typically developing children [30]. These results suggest that the control of upright stance in children with CP is altered.

Balance impairments limit motor development for children with CP. In one study [31], the relationship between postural control and motor ability, as measured by a functional assessment of dynamic tasks that mirror activities of daily living, was assessed. A significant inverse correlation was found between gross motor developmental ability and sway while standing with eyes closed for fifteen children with CP, twelve of which were spastic. After measuring sway area with eyes open, eyes closed, with swaying vision, and with swaying vision and sway support, sway area during the eyes closed condition was found to be the best predictor of this motor

ability (r = -0.76, $p < 0.01$). The strength of this relationship would indicate that somatosensory and/or vestibular deficits, in turn increasing reliance on vision for postural control, drive observed impairments in motor function. These findings led the authors to conclude that postural control with proprioception and vestibular mechanisms may be limiting factors of motor ability in children with CP.

The development of postural control during dynamic tasks involves an improvement in the specificity and organization of muscle responses to maintain balance. This organized response is typically characterized by a distal to proximal onset, where muscles in the stretched ankle (e.g., tibialis anterior or gastrocnemius) are activated first, followed by the quadriceps and abdominal muscles at a slight delay. In a longitudinal study [32], the development of independent balance abilities was assessed in typically developing children from infancy to the independent walking stage. Balance perturbations in the form of unexpected platform translations were delivered to infants at various stages. Testing began when the infant was not yet able to pull-to-stand using an external support (2-6 months) and continued until this skill was attained, along with independent stance and walking skills (18 months). It was found that in the pre-pull-to-stand stage, infants showed an uncoordinated muscle response organization with perturbations to their balance, characterized by co-activation of antagonist muscles and a non-distal to proximal onset. When these infants reached the pull-to-stand and independent walking stages, directionally appropriate muscle responses emerged. Additionally, co-activation of antagonist muscles during the response was reduced with development [32].

The coordinated muscle response to a perturbation is underdeveloped in children with CP compared to typically developing children [30]. To compare these

two groups, the same platform translation model was used to study the neural response before and after independent walking had been achieved [33]. In the pre-walkers, both typically developing children and those with CP displayed an unorganized muscle response pattern with co-activation of antagonist muscles. These results were not surprising given that an organized response pattern is typically not fully developed at this stage. In the walkers, however, it was found that children with CP did not develop the characteristic distal-to-proximal muscle response like their age-matched controls. Instead, the children with CP would co-activate their distal and proximal muscles, as well as co-activate antagonist muscles at a greater degree than controls. Described as a crouched posture, the initial position that children with CP assume prior to the balance perturbation may be the cause for their unique, neuromuscular response with postural control. To directly assess the influence of crouched posture, control subjects were asked to stand in a crouched posture that mimicked that of children with CP. In this posture, the neural response of the TD children more closely matched those of the CP children, with increased co-activation of antagonist muscles and onset latencies similar to those of the CP subjects [33].

Children with CP have an abnormal neuromuscular response to perturbations of balance. This skill was first explored in children with CP by perturbing balance with a moveable platform and analyzing the neuromuscular response by measuring surface electromyography (EMG) of the lower extremities [5]. Ten children with CP who were able to ambulate independently were compared to ten, age-matched controls, where it was found that the CP group had significantly longer muscle onset latencies and higher co-contraction about the ankle. In a separate study on the neuromuscular response of children with CP to balance perturbations, no significant

differences were found in onset latencies or co-contraction levels. In addition, it was observed that children with CP were not able to scale the amplitude of their neuromuscular response with increasing balance perturbation intensities [6]. Given the inconsistent results across studies, further exploration of the neuromuscular response to balance perturbations is warranted to discover what aspects are affected in children with CP relative to typically developing counterparts.

2.5 Musculoskeletal Development and Fracture Risk

Children with CP have a significantly underdeveloped musculoskeletal system that puts them at a high risk for fractures, particularly of the lower extremities. In non-ambulatory children with CP, there is significant underdevelopment of trabecular bone microarchitecture in the distal femur [12]. In addition, the femoral midshaft is thin with very thin cortical walls, leading to significantly lower estimates of bone strength relative to their typically developing peers [13]. Even in ambulatory children with mild, spastic CP, there is significant underdevelopment of bone architecture and low bone strength in the midtibia [14]. Both non-ambulatory and ambulatory children with CP also display smaller and weaker muscles of the lower extremities, along with greater fatty infiltration of the bone marrow and surrounding skeletal muscle [10, 14].

Low-energy fractures to the lower extremities are a major cause of injury for children with CP [34, 35]. In fact, 28% of children with quadriplegic cerebral palsy who are non-ambulatory experience a fracture before adulthood, with 80% of those fractures in the lower extremities [36]. The underdeveloped musculoskeletal system in conjunction with a high fall risk likely explains why nearly half of all femur fractures in children with CP is due to a fall [37].

2.6 Physical Activity Levels and Chronic Disease

Balance deficits may be one of the main barriers to sufficient levels of physical activity in children with CP. In typically developing children, physical activity counts were found to be 5.6-fold higher than children with quadriplegic cerebral palsy [10]. In the highest functioning group of children with CP (GMFCS Level I), there were still significantly lower levels of physical activity when compared to their typically developing peers ($p = 0.04$) [38]. In a study on the difference in Pediatric Balance Scale scores between GMFCS levels I – III [39], there was a significant difference ($p < 0.05$) among the three GMFCS levels tested. A post-hoc analysis revealed significant differences among all three levels. This would indicate that lower functioning children with CP have poorer balance, which could be a factor in the lower physical activity levels observed in other studies. In fact, in this same study, a significant correlation ($r = 0.639$, $p < 0.001$) was found between the Pediatric Balance Scale scores and the participants' PEDI (pediatric evaluation of disability inventory) motor performance scores, which represents the types of activities (i.e., running, jumping) a child does in his or her environment according to a parent or guardian. This correlation indicates that children with better functional balance, according to the Pediatric Balance Scale, also engage in more complex movements. These results support the importance of balance to physical activity.

In addition, adults with CP have significantly higher odds of chronic diseases compared to healthy adults (*95% C.I.* > 1 for all chronic diseases except diabetes), with a large percentage of individuals losing mobility with age due to a breakdown of muscle tissue or joint pain [15].

2.7 Assessments of Fall-Recovery Ability

While sway-based measures may differentiate static balance abilities between groups, postural steadiness during quiet stance is not strongly or consistently correlated with the ability to recover balance following a perturbation in older adults [40 – 42]. In addition, sway-based measures have been shown to be poor predictors of fall risk in both older adults and individuals with neuromuscular disease [43 – 45]. As a result, the information provided by these assessments may not be enough to comprehensively characterize fall risk in children with CP. As a result, balance assessments of fall recovery may provide more information on differences in fall risk between children with CP and typical development. The ability to prevent or minimize a step after an induced fall can be objectively quantified with single-stepping thresholds [9]. These thresholds, defined as the disturbance magnitudes that consistently elicit a protective step, have been prospectively related to falls in older adults. In a study of 112 ambulatory, community-dwelling older women, a standard-deviation decline in posterior single-stepping thresholds was associated with a 55% greater likelihood of being a faller (OR [95% C.I.] = 1.55 [1.04 – 2.30]), and was also associated with a greater number of falls in the subsequent year (OR [95% C.I.] = 1.29 [1.02 – 1.63]) [Crenshaw et al., *In Review*]. Previous studies [5, 6] have used balance perturbations to assess reactive balance control in children with CP, but they did not measure the ability to prevent a step. Instead, balance perturbations were scaled to body size, and the impaired neural response associated with CP was the main focus of the analysis. Stepping thresholds represent a measure that, importantly, quantifies an outcome that may result from such neuromuscular impairment. In other words, we cannot assume that an altered neuromuscular response has a meaningful influence on the outcome of the recovery response.

While stepping thresholds reflect a transition in the fall recovery strategy (i.e., stepping or not), and electromyography (EMG) measures provide insight on the neuromuscular response, the margin of stability (MoS) measure directly quantifies dynamic stability throughout the fall-recovery response [46 – 48]. The MoS, which has units of length, is a dynamic measure that accounts for the whole body center of mass position *and* velocity (extrapolated center of mass) relative to the standing base of support.

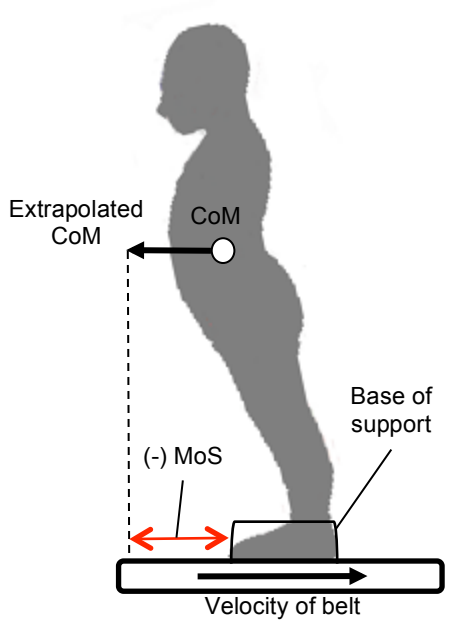

Figure 3. Model representing margin of stability (MoS) calculation, where the center of mass (CoM) position and velocity are represented as the extrapolated CoM, the vertical projection of which falls outside of the base of support, resulting in a (-) MoS.

A stable situation (+MoS) is defined as one in which a person should theoretically be able to remain upright without stepping. This stability is maintained by modulating the vertical ground reaction force under the base of support. An

unstable situation (-MoS) is defined as one in which upright stance should theoretically be impossible to maintain using such a strategy (Figure 3). In unstable situations, a fall must be arrested by stepping, providing an external force (e.g., using a hand rail), or utilizing a counter-rotation strategy to enact shear ground reaction forces (e.g., swinging the arms) [49]. As such, this measure is proportional to the impulse needed to change stability states [46].

2.8 Interventions to Improve Fall-Recovery

The importance of quantifying and identifying underlying mechanisms behind balance deficits in children with CP lies in the potential for revealing new and modifiable targets for interventions to reduce fall risk. Given the interdependence of balance on inactivity, such interventions could increase physical activity levels and reduce the risk of chronic disease. The contribution of difficulties in proprioceptive mechanisms and organized muscle responses to deficits in balance is clear, both statically and dynamically. Thus, an appropriate next step is to identify interventions that would improve these factors by removing the barriers to normal function, such as spasticity. In addition, exploring interventions that have benefitted both the static and dynamic balance abilities of other populations who experience high levels of spasticity about the ankle would be beneficial. One such example of this is whole-body vibration therapy.

Whole-body vibration therapy has been shown to reduce spasticity in children with CP. In a study by Katusic and colleagues, the effects of whole-body vibration on spasticity were studied in eighty-nine children with CP [50]. GMFCS levels ranged from II to V, and children were divided into control or intervention groups. The control group received physical therapy only and the intervention group received a

combination of physical therapy and whole-body vibration therapy over twelve weeks, with 3 sessions of 40 minutes per week. Spasticity, estimated according to the Modified Ashworth Scale, was significantly reduced in the intervention group compared to the control group. It has been hypothesized that whole-body vibration leads to altered connectivity between corticospinal cells and motor neurons. During whole-body vibration, proprioceptive pathways are being constantly and strongly stimulated, activating the sensory receptors used in reflexive muscle contractions. After several weeks of this treatment, proprioceptive feedback may become more efficient, leading to more effective and appropriate stretch responses [51]. It is unknown whether this translates into improved balance abilities for children with CP. Whole body-vibration therapy has been shown to improve postural control for individuals with multiple sclerosis [52], which is another population that commonly experiences spasticity.

Another intervention for improving fall-recovery in children with CP that has shown to be effective in other populations with neuromuscular deficits is perturbation-based fall-recovery training. This type of intervention, which involves repeated practice of responding to external perturbations, has been shown to reduce the risk of falling (*risk ratio* 0.71, *95% CI* 0.52 – 0.96) in both older adults and individuals with Parkinson's disease [53]. A study that implemented repeated slips to individuals with stroke, another population with central nervous system injury, found that the fall-recovery response was modifiable, characterized by a more stable position both before and after a recovery step was taken [54]. Postural control mechanisms have also been demonstrated to be modifiable in children with CP, where reactive balance training for one week resulted in less sway and a faster time to stabilization after a perturbation

[55]. This evidence suggests that the fall-recovery response can be ameliorated for this population.

2.9 Conclusion

In conclusion, balance deficits in children with CP are a likely contributor to their decreased physical activity levels, either directly by preventing activity without falls or indirectly by causing fractures and a fear of falling. It appears that these balance deficits can be attributed to altered corticospinal projections that lead to spasticity and high levels of co-contraction. These abnormalities negatively affect postural control mechanisms that are necessary for effective static and dynamic balance abilities utilized during physical activity. For this reason, a vital next step in improving the well being of children with CP is exploring interventions that can enable physical activity by improving balance and decreasing fall risk.

Chapter 3

MANUSCRIPT

3.1 Introduction

Cerebral palsy (CP) is a non-progressive neurological disorder that arises from an injury to the brain, typically at infancy. The resulting impairments of muscle coordination, movement, and balance likely underlie the high annual incidence of falls reported for adults with CP (97%) [4] compared to that of unimpaired adults (20%) [56]. While the fall incidence for children with CP is not documented, such motor impairments likely predispose them to falls. A high risk of falls, in conjunction with low areal bone mineral density and a markedly underdeveloped architecture in the midshaft [13] and distal end [14] of their femur, places children with CP at a higher risk of fractures. Nearly half of all femur fractures in children with CP are due to a fall [40]. Both falls and fractures lead to decreased physical activity levels [3, 4], which are 44% lower for children with mild, spastic CP relative to children with typical development (TD) [10, 14]. Decreased physical activity levels lead to further unloading of the skeleton and declines in motor function [11], exacerbating the risk for falls and fractures. Ultimately, decreased levels of activity can lead to an increased risk of chronic disease [15]. The risk of falls and fall-related injury, therefore, represents a critical barrier to enabling physical activity and preventing chronic disease for children with CP.

Balance in children with CP has typically been assessed using quasi-static measures of standing sway or clinical assessments such as the Pediatric Balance Scale,

a derivative of the Berg Balance Scale [57]. The utility of these measures in assessing fall risk is limited, however. Both postural sway and the Berg Balance Scale do not sensitively predict falls in older adults and individuals with neuromuscular disease [43 – 45]. A limitation of clinical balance tests and standing sway measures is that they do not evaluate the response to an externally induced fall. In older adults, the ability to prevent or minimize the number of steps after a standing postural disturbance has been prospectively related to falls [58, 59]. Fall-recovery measures have been weakly correlated with postural sway and functional measures [40, 41]. Evaluating the fall-recovery response, therefore, may provide relevant insight on how CP alters fall risk that cannot be detected from other measures of sway or balance.

The ability to recover from a fall can be objectively quantified with an assessment of anterior and posterior single-stepping thresholds [9], or the disturbance magnitudes that consistently elicit a forward or backward protective step, respectively. Stepping thresholds decline with middle and old age [47], which is accompanied with an increased risk of falls [60] and fall-related injury [61]. In older adult women, a standard deviation decline in posterior stepping thresholds was associated with a 55% greater likelihood of falling (Crenshaw et al., *In Review*). This evidence suggests that stepping thresholds are a valid indicator of fall risk. To date, the effects of CP on such thresholds have not been evaluated. Comparing the thresholds of children with and without CP would specifically quantify the detrimental effects of CP on the ability to recover from a fall.

Stepping thresholds quantify the ability to respond to postural disturbances without a step. Further biomechanical analyses, however, are needed to identify the underlying mechanisms of impaired performance. Using motion capture technology,

we can quantify the resulting dynamic stability of the fall-recovery response. The margin of stability (MoS) is a spatial measure of dynamic stability that accounts for the whole-body center of mass (CoM) position and velocity relative to the base of support [46]. The MoS has been utilized in studies of fall-recovery ability, serving as a possible mechanistic variable to explain fall-risk in older adults [47, 48, 59]. Here, a stable situation (+MoS) is defined as one in which a person should theoretically be able to remain upright without stepping. This stability is maintained by modulating the vertical ground reaction force under the base of support. In unstable situations (-MoS), a fall must be arrested by stepping, providing an external force (e.g., using a hand rail), or utilizing a counter-rotation strategy to enact shear ground reaction forces (e.g., swinging the arms) [49]. By quantifying the resulting dynamic stability of the fall-recovery response, we are able to determine if CP is associated with a greater loss of stability after a perturbation. Alternatively, we may observe that CP impairs the ability or willingness to recover from dynamically unstable situations without a step.

Another potential underlying mechanism of an impaired fall-recovery response is an altered muscle response, as assessed by surface electromyography of the lower extremity musculature. In response to anteroposterior balance perturbations, children with CP are characterized by a delayed muscle activation of the ankle plantarflexors and dorsiflexors, increased co-contraction about the ankle, and an inability to scale the muscle response to the disturbance magnitude [5, 6]. A muscle response that is delayed, diminished, or characterized by co-contraction could lead to lower stepping thresholds.

The purpose of this pilot study was to assess differences in the response to an external postural disturbance between children with CP and children with TD. It was

hypothesized that children with CP would have an impaired fall-recovery response, as characterized by lower anterior and posterior single-stepping thresholds. In order to investigate possible underlying mechanisms of our hypothesis, we evaluated the resulting dynamic stability and neuromuscular response of the ankle plantarflexors and dorsiflexors.

3.2 Methods

3.2.1 Participants

Three ambulatory children with spastic CP (2 hemiplegic, 1 diplegic; 2 males, 1 female; mean age 10 years 7 months, SD 3 years, range 6 years 6 months to 12 years 11 months) who were GMFCS (Gross Motor Function Classification System) levels I-II were recruited from the CP Program at the AI duPont Hospital for Children in Wilmington, DE. Fourteen children with typical development (6 males, 8 females; mean age 9 years 3 months, SD 2 years, range 5 years 10 months to 11 years 5 months) were recruited from the Newark area of Delaware. Approval for this study was obtained from the Institutional Review Board at the University of Delaware (Appendix A). Written informed consent was provided by a legal guardian of each participant, and written informed assent was provided by participants.

3.2.2 Instrumentation

Kinematics

Participants were outfitted with 41 retro-reflective markers placed on their extremities, pelvis, trunk, and head. The trajectories of these markers were recorded by up to 13 cameras (Motion Analysis Corporation, Santa Rosa, CA; 120 Hz).

Electromyography

The neuromuscular response was recorded using surface electromyography on the lower extremities (Delsys, Inc., Natick, MA, 600 - 1200 Hz), where four wireless bipolar surface electrodes were placed bilaterally on the medial gastrocnemius (MG) and tibilias anterior (TA). Sensors were oriented in the direction of the muscles' fibers and at half the distance between the motor endpoint and the distal end of each muscle [62]. Limb dominance was determined by asking the participants, "which leg would you kick a ball with?", and confirming with the parent or guardian.

3.2.3 Measurements

Physical characteristics

Height and body mass were measured while participants wore minimal clothing and without shoes or braces. Height was measured using a stadiometer (Seca, Chino, CA) to the nearest 0.1 cm and body mass was measured using a scale (Detecto, Webb City, MO) to the nearest 0.1 kg.

Pediatric Balance Scale

Functional balance was assessed by research staff using the Pediatric Balance Scale (Appendix B). Participants were lead through a series of 14 tasks that mirrored activities of daily living (i.e. moving between chairs), and a research assistant scored each task on a scale of 0 – 4.

Postural sway

Quasi-static postural control was assessed by measuring the trajectory of the center of pressure while participants stood shoulder width apart on a force plate

(Advanced Mechanical Technology, Inc., Watertown, MA; 600 - 1200 Hz) under 2 conditions: eyes open and eyes closed. Participants were instructed to "stand as still as possible for 30 seconds", and completed one trial of each condition. Participants were told to look straight ahead at an image approximately 10 feet away. Path length was calculated as the total CoP displacement during the 30-second trial. A Romberg ratio was calculated by dividing the eyes closed by the eyes open path length [63].

Single-stepping threshold

Participants stood on a computer-controlled treadmill (ActiveStep, Simbex®, Lebanon, NH, Figure 4) while wearing a safety harness (DMM, Wales, UK). This harness was attached to an overhead rail and adjusted as to prevent contact of the knees or hands with the treadmill should a fall occur. Participants were instructed to "try not to step" in response to rapid treadmill belt accelerations comprised of 400 millisecond surface translations. These disturbances were characterized by a triangular waveform velocity profile consisting of 200 ms acceleration and deceleration phases. Beginning at an initial treadmill belt acceleration of 0.5 m/s^2, a progressively challenging series of disturbances was applied. Posterior and anterior belt accelerations, inducing backward and forward sway, respectively, were delivered in a pseudo-randomized order. In other words, the direction of the disturbance was randomly determined for each trial, with the constraint that no more than four consecutive trials could be delivered in the same direction. For subsequent disturbances, the initial acceleration was increased or decreased in increments of 0.5 m/s^2 depending on success or failure. Failure was defined as either taking a step or using the harness to support greater than 20% of the participant's body weight as

recorded by a force transducer (Dillon, Fairmont, MN) above the harness. Anterior and posterior single-stepping thresholds were identified as the initial acceleration that resulted in four consecutive failed responses [9]. The series of disturbances was continued until both anterior and posterior thresholds were determined, represented by the initial belt acceleration for each respective threshold.

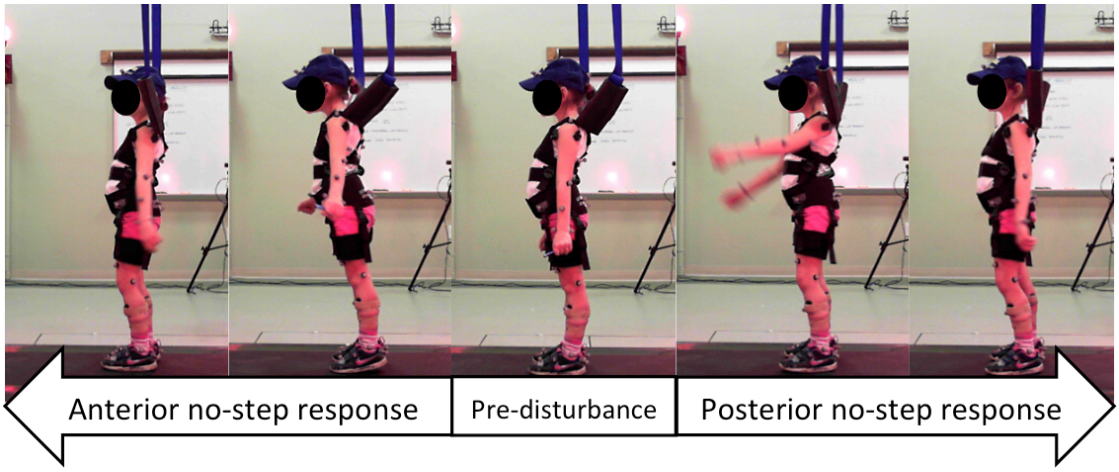

Figure 4. Single-stepping threshold protocol setup: 6 year-old child with cerebral palsy standing on the computer-controlled treadmill prior to disturbance onset (Pre-disturbance), successfully reacting to an anterior balance perturbation (2 m/s^2) (Anterior no-step response), and successfully reacting to a posterior balance perturbation (1.5 m/s^2) (Posterior no-step response).

A simple inverted pendulum model was used to express thresholds as the ankle torque (τ) necessary to counter the treadmill belt acceleration:

$$\tau = |m \cdot a \cdot 0.586 \cdot h| \qquad [1]$$

where m is body mass, a is the initial acceleration of the treadmill belt, and $0.586 \cdot h$ is the estimated inverted pendulum length based on subject height (h) [64]. Here, thresholds expressed as torque represents the estimated magnitude of the disturbance

on the participant, as the force delivered by the treadmill likely varies as a function of body size. Thresholds expressed as acceleration values, then, represent disturbance magnitudes that are scaled to body size.

3.2.4 Analysis

Custom LabVIEW software (National Instruments, Austin, TX) was developed to calculate the following biomechanical and neuromuscular mechanisms:

Biomechanical mechanism

Using motion analysis data, dynamic stability was quantified as the MoS [46, 47]:

$$MoS = d + \frac{v}{\sqrt{\frac{g}{l}}} \qquad [2]$$

where $d = x_{toe} - x_{CoM}$ (x is the anteroposterior position) and $v = v_{toe} - v_{CoM}$ (v is velocity) for anterior disturbances, and $d = xCoM - xheel$ and $v = v_{CoM} - v_{heel}$ for posterior disturbances. The CoM position was calculated from kinematic data and documented anthropometric values [65]. The term, g represents gravity (9.81 m/s^2), and l is the sagittal plane distance between the mean ankle joint center location and whole body center of mass calculated throughout the trial. For the trials representing the highest disturbance magnitude in which a step was prevented, the minimum MoS after disturbance onset was calculated.

Neuromuscular mechanism

The plantarflexor and dorisflexor muscle activity was assessed for the trials representing the largest anterior and posterior disturbances after which a step was not taken. Muscle onset latency, peak muscle activation, and co-contraction index (CCI)

were calculated using custom software (LabVIEW; Figure 5). Unfiltered EMG signals were shifted to account for a 48-millisecond delay between EMG sensors and kinematic data (as per Delsys equipment documentation). The signals were then de-meaned, bandpass filtered (10 – 300 Hz), rectified, and lowpass filtered (8th order Butterworth) at 50 Hz for muscle onset latency and 4 Hz for peak activation and co-contraction index (Figure 5). A higher frequency cutoff was used for muscle onset latency due to the effect of filtering on time-based measures of muscle activity [66]. The latency and magnitude of the muscle response was determined for the agonist muscles of both legs (i.e. the MG for anterior disturbances and TA for posterior disturbances). Muscle onset latency was defined as the time after disturbance onset at which muscle activity exceeded three standard deviations above the median activity 500 milliseconds before disturbance onset, and was sustained for at least 50 milliseconds. Peak muscle activation was calculated as the maximum amplitude achieved by the agonist muscle within one second of disturbance onset, normalized to pre-disturbance median activity. Co-contraction index (CCI) was defined as the average concurrent activity between the agonist and antagonist muscles, normalized to pre-disturbance median activity, for 500 milliseconds after disturbance onset [67]:

$$\sum_{0}^{500\ ms}\left(\frac{antagonist}{agonist}\right)\times(agonist+antagonist) \qquad [3]$$

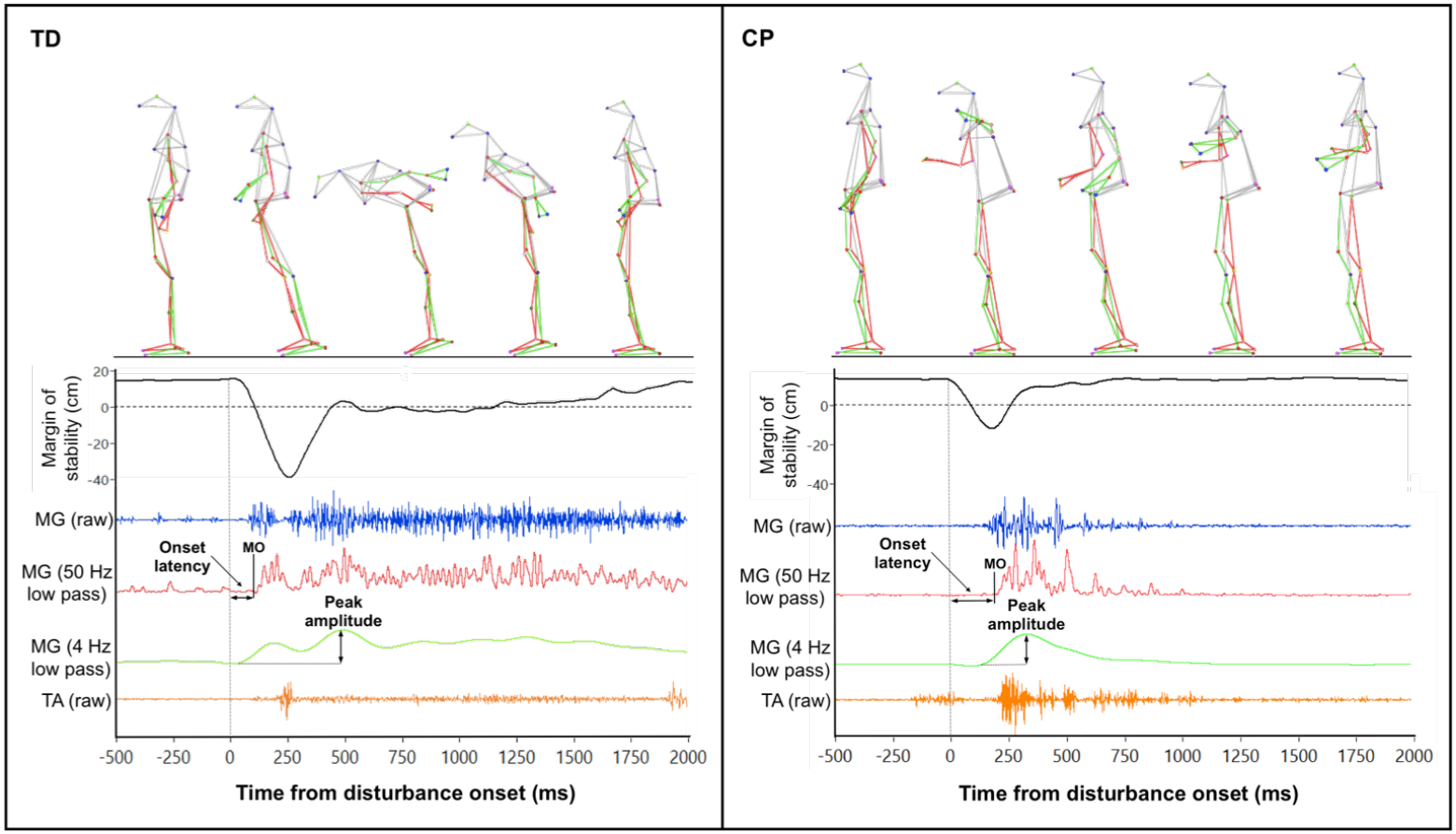

Figure 5. The margin of stability and neuromuscular response during successful recovery from a 6 m/s^2 (188 Nm) anterior perturbation by an 11 year-old typically developing child (TD) compared to the same response variables during successful recovery from a 3 m/s^2 (129 Nm) anterior perturbation by a 12 year-old child with cerebral palsy (CP). MO, muscle onset; MG, medial gastrocnemius; TA, tibialis anterior.

Statistics

The intent of this pilot study was to demonstrate between-group effects that warrant further investigation with a larger sample. Therefore, group differences in physical characteristics and all measures of balance were evaluated using effects sizes (Cohen's *d*). In addition, given the inability to assume normal distribution due to the small sample size, Mann-Whitney *U* tests were conducted with a significance level set at $\alpha = 0.05$. Data were evaluated using SPSS (v24, IBM, Armonk, NY).

3.3 Results

Physical characteristics

No significant differences were found in the physical characteristics between groups ($p > 0.05$ for all measures; Table 1). There were large effect sizes, however, for height percentile ($d = 1.075$) and body mass percentile ($d = 0.882$), with the CP group being shorter and having less mass. Still, all individuals for both groups fell within the 5^{th} and 95^{th} percentile of BMI.

Table 1. Descriptive statistics of cerebral palsy (CP) and typically developing (Con) groups.

	CP (n = 3)	Con (n = 14)	*p*	*d*
Physical characteristics				
Age (y)	10.6 ± 3.5	9.2 ± 1.9	0.300	0.632
Sex (male/female)	2/1	6/8		
Race (W/B/H/O)	3/0/0/0	14/0/0/0		
Height (cm)	135.3 ± 22.2	135.1 ± 12.3	0.859	0.012
Height (%)	23 ± 27	53 ± 28	0.091	1.075
Body mass (kg)	32.2 ± 14.0	31.9 ± 7.7	0.768	0.016
Body mass (%)	30 ± 28	56 ± 30	0.244	0.882
BMI (kg/m^2)	16.9 ± 2.2	17.2 ± 2.2	0.859	0.162
BMI (%)	45 ± 31	55 ± 32	0.432	0.319
GMFCS (I/II)	1/2	-		

Group comparisons were made using independent *t* tests unless otherwise noted. Values are means ± SD. % reflects the percentile relative to sex- and age-based norms. W- White; B- Black; H- Hispanic; O- Other; GMFCS- Gross Motor Function Classification System.

Pediatric Balance Scale

Children with CP displayed compromised balance compared to children with TD, as evident by lower PBS scores ($p = 0.003$). Children with TD consistently achieved a maximum score of 56, while children with CP had a range from 50 – 54 (Figure 6).

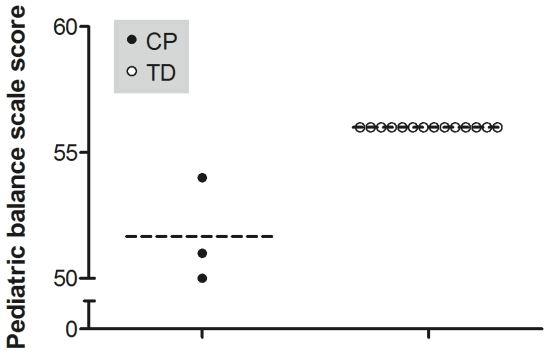

Figure 6. Pediatric balance scale scores for children with CP (closed circles) and TD (open circles), where the maximum possible score is 56.

Postural sway

Moderate to large differences were found in path length between groups for both eyes open ($d = 0.635$, $p = 0.305$) and eyes closed ($d = 1.379$, $p = 0.229$) conditions (Figure 7A). There was a substantial difference in Romberg ratios between groups as well ($d = 1.478$, $p = 0.114$; Figure 7B).

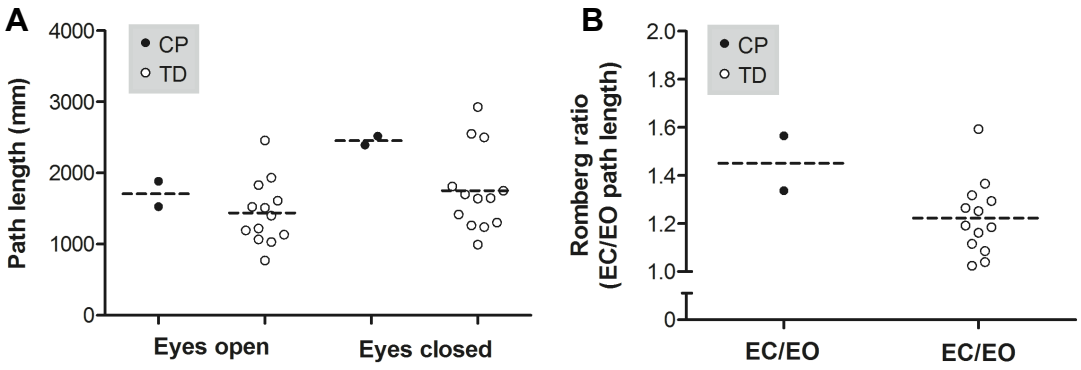

Figure 7. (A) Path length, or total center of pressure excursion in mm, during tasks of quiet standing with eyes open and eyes closed, and (B) Romberg ratio for children with CP (closed circles) and TD (open circles). Note: CP (n = 2) and TD (n = 13) due to equipment malfunctions for one subject in each group.

Single-stepping thresholds

There were large differences in the anterior thresholds when expressed as acceleration ($d = 2.579$, $p = 0.003$; Figure 8A) and moderate differences when expressed as ankle torque ($d = 0.813$, $p = 0.300$; Figure 8B). An analysis of the minimum MoS at each group's respective anterior threshold levels indicated a moderate difference between groups ($d = 0.808$, $p = 0.300$; Figure 9), where children with typical development were able to recover from more dynamic instability without a step.

A similar trend was seen for posterior thresholds, with large differences when expressed as acceleration ($d = 1.556$, $p = 0.047$; Figure 8A) and moderate differences when expressed as ankle torque ($d = 0.580$, $p = 0.300$; Figure 8B). The associated minimum MoS values were substantially different between groups ($d = 1.049$, $p = 0.032$; Figure 9), where children with typical development displayed a greater ability to recover from dynamic instability in the posterior direction as well.

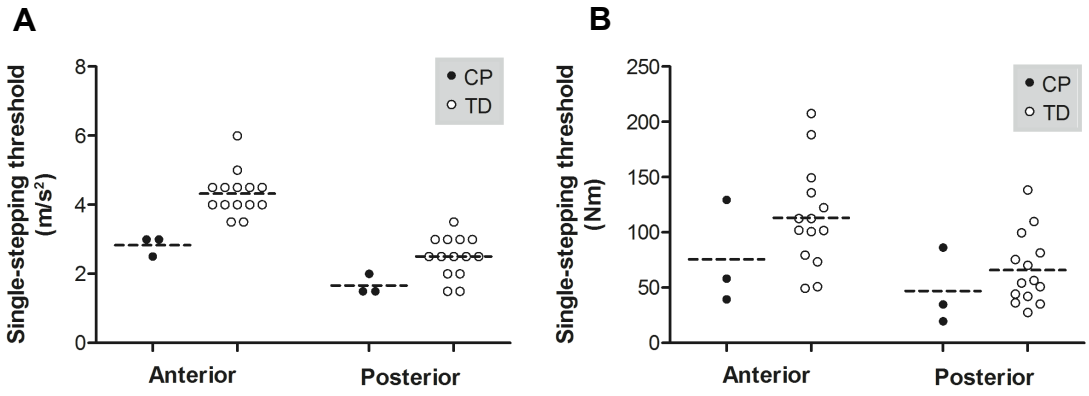

Figure 8. Anterior and posterior thresholds for children with CP (closed circles) and TD (open circles) presented as the (A) initial belt acceleration and (B) ankle torque necessary to prevent a step at the acceleration where a subject failed four consecutive times.

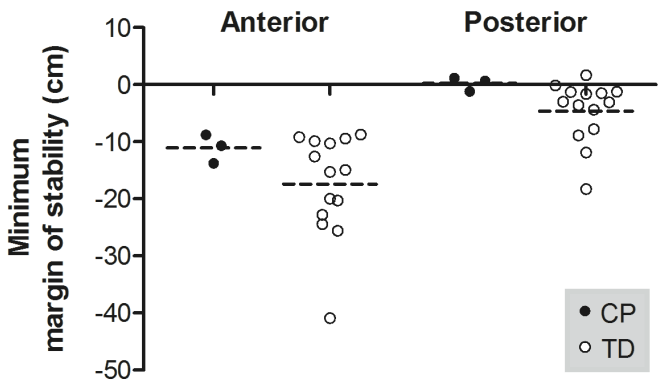

Figure 9. Minimum margin of stability (MoS) at the highest perturbation level for which a step was prevented for children with CP (closed circles) and TD (open circles).

Neuromuscular response

Children with CP displayed longer muscle onset latencies of the agonist muscles for both the anterior (dominant: $d = 2.565$, $p = 0.033$; non-dominant: $d = 2.188$, $p = 0.019$; Figure 10A) and posterior (dominant: $d = 2.528$, $p = 0.033$; non-dominant: $d = 2.018$, $p = 0.033$; Figure 10B) direction relative to the typically developing group.

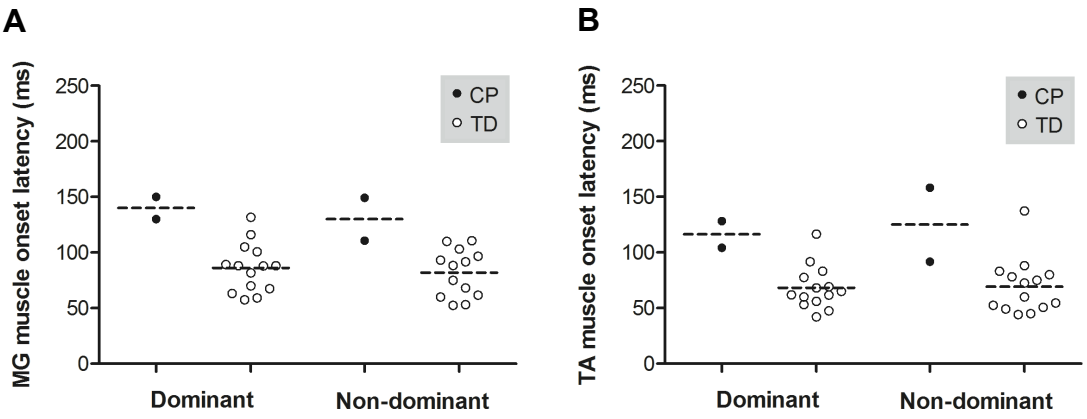

Figure 10. Agonist muscle onset latencies (ms) for the anterior (A) and posterior (B) direction for children with CP (closed circles) and TD (open circles). MG, medial gastrocnemius; TA, tibialis anterior. Note: CP (n = 2) and TD (n = 13 for non-dominant MG) due to equipment malfunctions for one subject in each group.

There was no clear difference in the muscle activation amplitude for the MG (agonist muscle) with anterior disturbances (dominant: d = -0.308, p = 0.500; non-dominant: d = 0.115, p = 1.000; Figure 11A). Muscle activation amplitude for the TA (agonist muscle) with posterior disturbances (dominant: d = 1.596, p = 0.067; non-dominant: d = 1.763, p = 0.017; Figure 11B) was lower in children with CP than controls.

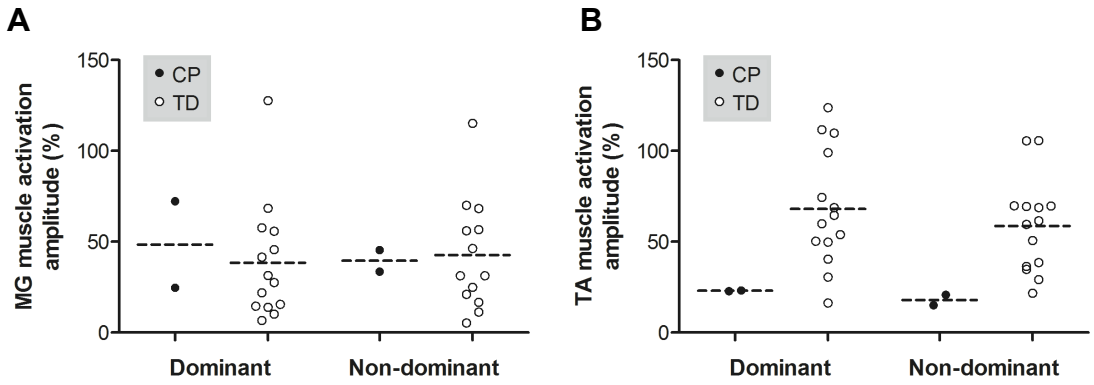

Figure 11. Agonist muscle activation amplitude for the anterior (A) and posterior (B) direction for children with CP (closed circles) and TD (open circles). MG, medial gastrocnemius; TA, tibialis anterior. Note: CP (n = 2) and TD (n = 13 for non-dominant MG) due to equipment malfunctions for one subject in each group.

Co-contraction of the agonist-antagonist muscles showed some moderate differences in the anterior direction (dominant: d = -0.491, p = 0.817; non-dominant: d = -0.605, p = 0.476; Figure 12A), with the CP group having lower co-contraction. In the posterior direction, children with CP had higher co-contraction of their dominant limb (d = 0.691, p = 0.267), with no clear difference in the non-dominant limb (d = 0.078, p = 0.476) (Figure 12B).

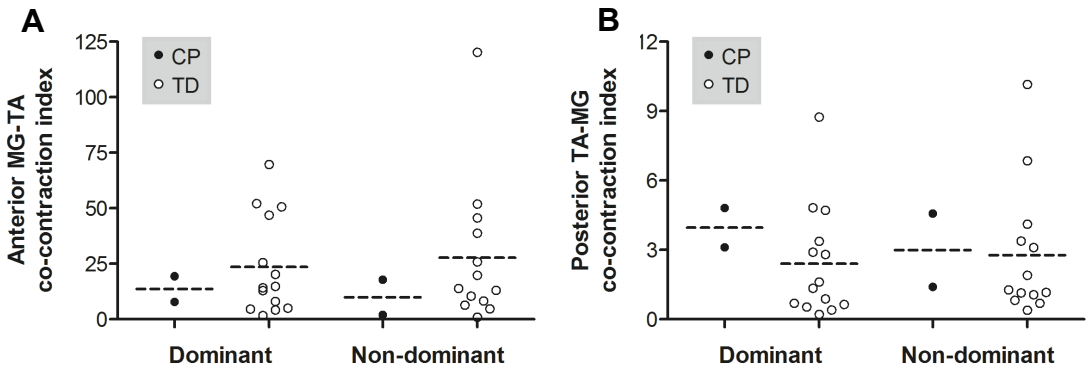

Figure 12. Agonist-antagonist muscle co-activation index for the anterior (A) and posterior (B) direction for children with CP (closed circles) and TD (open circles). MG, medial gastrocnemius; TA, tibialis anterior. Note: CP (n = 2) and TD (n = 13 for non-dominant limb) due to equipment malfunctions for one subject in each group.

3.4 Discussion

The purpose of this pilot study was to assess differences in the fall-recovery response between children with CP and children with typical development. It was hypothesized that children with CP would have an impaired response to balance perturbations, as characterized by lower anterior and posterior single-stepping thresholds. The results of this study have supported our original hypothesis with lower single-stepping thresholds in both directions for children with CP than typically developing controls. The lower stepping thresholds coincided with less-negative minimum MoS, or less instability, at the respective thresholds. This is an indication that children with CP are not effectively utilizing counter-rotation mechanisms or the deceleration of the belt to recover from the perturbations to balance. We do not know if they are *unable* or *unwilling* to use these strategies to recover from such dynamic instability. In a study of 112 older adult women, single-stepping thresholds were significantly, but weakly correlated with measures of balance confidence ($r = 0.19$ –

0.20; Crenshaw, et al., In Review). The influence of balance confidence may be greater for children with CP, a population that likely has a higher fall rate than that of community-dwelling older women. To date, however, there are no validated measures of balance confidence for children.

In the present study, investigation of the neuromuscular response to a balance perturbation revealed clear differences between groups. In children with CP, both the plantarflexors and dorsiflexors of the dominant and non-dominant limbs displayed a delayed onset as agonist muscles. Specifically, the observed latency times ranged from 110 – 160 ms for children with CP and 50 – 100 ms in typically developing children. Previous studies [5, 6] did not observe a faster onset for typically developing children, but instead observed similar onset latencies between groups. This discrepancy may be explained by the neuromuscular response that is being elicited. For previous studies [5, 6], a common disturbance level was delivered for both groups. While this may result in a true threat to balance for children with CP, the same disturbance level may not require a full effort from the typically developing participants. In other words, a fast muscle onset was not necessary for the typically developing children to maintain their balance. In this study, however, the neuromuscular response elicited was relative to their balance ability. The onset latencies we found in our typically developing participants are supported by their similarity to those observed in young, healthy adults with treadmill acceleration impulses [68, 69]. While it is difficult to interpret the exact profile of balance perturbations used in previous studies, we can compare the reported characteristics to our perturbation profile. For example, in one study [6], the maximum displacement velocity reached for both children with CP and typically developing children was 0.75 m/s. In our study, twelve of the fourteen typically

developing participants were able to prevent a step at velocities over 0.75 m/s, with some reaching over 1.0 m/s. As a result, the balance perturbations in this previous study may not have been appropriately scaled for typically developing children.

Peak activation amplitude of the MG for anterior disturbances showed no apparent differences in either limb between groups. The TA, however, had substantially lower amplitudes for children with CP in both the dominant and non-dominant limbs. While this may be an indication that children with CP are unable to produce a large response of their dorsiflexors, it is important to consider how the data was analyzed. Activation amplitudes were normalized to pre-disturbance activity, meaning high activity of the TA prior to disturbance onset may be dampening the observed response in the CP group. Co-contraction levels of both the dominant and non-dominant limb for anterior disturbances were lower for children with CP. Effect sizes were only moderate and this difference may be due to the low sample size of children with CP. In the posterior direction, co-contraction was higher for children with CP, but only by a moderate amount. The small differences in co-contraction between groups is consistent with previous studies [5, 6]. Based on the findings of this study, it appears that children with CP have a delayed and dampened neuromuscular response to balance perturbations, which negatively affects their ability to recover from dynamic instability.

The pathophysiology behind the impaired response in children with CP is unclear, but may be related to issues of spasticity and proprioception. Individuals with CP who experience spasticity have an imbalance between excitatory and inhibitory neural impulses. It is believed that this imbalance is due to a lack of inhibitory signals as a result of damage to descending tracts from the brain, leading to a relative excess

of excitatory impulses and increased muscle tone [20]. For this to affect neuromuscular responses to balance perturbations, the observed, elicited response should involve some form of supraspinal control, as opposed to a stretch reflex response. The measured onset latencies of this study support that the observed responses do not solely represent monosynaptic stretch reflexes. The average latencies seen in both typically developing children (MG: 86 ± 22 ms, TA: 68 ± 19 ms) and those with CP (MG: 140 ± 14 ms, TA: 116 ± 17 ms) were at least 30 ms longer than the H-reflex latency. It is important to note, however, that these latencies include the mechanical delay of the translating surface and lengthening of the muscle, which could explain the extra 30 ms. This result is in agreement with other studies, where there was an absence of functionally relevant stretch reflex responses to balance perturbations [68, 70, 71].

Effective postural control relies on the integration of sensorimotor processes, including vision, vestibular, and proprioception. While it is possible for children with CP to have vision or vestibular deficits, it is likely that proprioception is negatively affected in this population due to the high prevalence of spasticity. Proprioception involves the input of mechanoreceptors in muscle and joints to sense the stationary position and movement of the limbs. Specifically, proprioception relies on signaling from muscle spindle receptors for changes in length and Golgi tendon organs for sensing contractile forces [24]. The common presentation of spastic muscle with volitional movements in CP may be hindering the processes necessary for muscle spindles and Golgi tendon organs to contribute to proprioception due to the effect of spasticity on their sensitivity. For this reason, the ability to sense position and movement of one's own limbs and body becomes more difficult. While it has not been

studied specifically in CP, spasticity has been shown to contribute to postural deficits in individuals with multiple sclerosis [27, 28]. The findings of this study add further evidence for the role of proprioceptive deficits in children with CP. The larger Romberg ratio in children with CP is indicative of a reliance on vision for balance, or an ineffective use of proprioception in postural control, which is in agreement with previous findings [2]. When viewed in conjunction with the compromised ability to recover from dynamic instability, there may be a causal relationship. In fact, we found moderate ($r = 0.486$, $p = 0.066$) to strong ($r = 0.552$, $p = 0.033$) correlations between the Romberg ratio and the minimum margin of stability in the anterior (Figure 13A) and posterior (Figure 13B) direction, respectively, when we combined the results from participants in both groups.

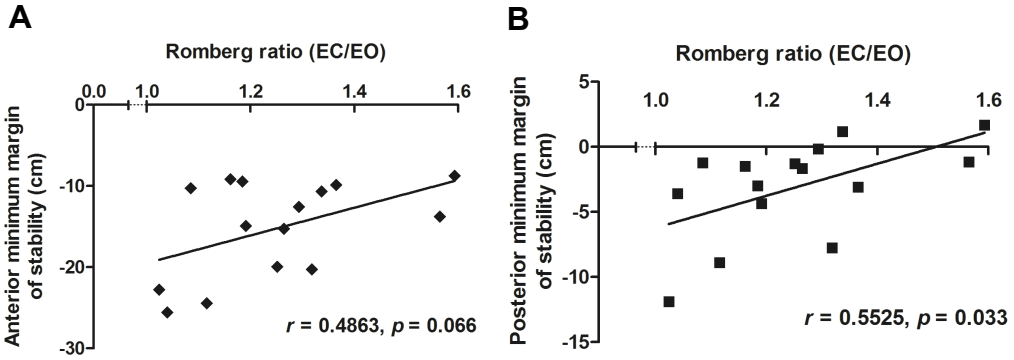

Figure 13. Relationship between (A) anterior and (B) posterior minimum margin of stability and the Romberg ratio (eyes closed path length/eyes open path length; EC/EO) for all participants from both groups.

The importance of connecting pathophysiological mechanisms to balance deficits in children with CP lies in the potential for revealing new and modifiable targets for interventions. Successful implementation of these interventions could

improve balance and reduce the risk of falls, in turn removing a barrier to physical activity. Based on the findings of this study, difficulties in proprioceptive mechanisms and effective muscle responses appear to contribute to balance deficits, both statically and dynamically. Thus, an appropriate next step is to identify interventions that would improve these factors by removing the barriers to normal function, such as spasticity. Whole body vibration therapy in conjunction with physical therapy has been shown to reduce spasticity in children with CP when compared to physical therapy alone [50]. Specifically, it has been hypothesized that WBV leads to altered connectivity between corticospinal cells and motor neurons. During WBV, proprioceptive pathways are being constantly and strongly stimulated, activating the sensory receptors used in reflexive muscle contractions. After several weeks of this treatment, proprioceptive feedback may become more efficient, leading to more effective and appropriate stretch responses [51]. It is unknown whether this translates into improved balance abilities for children with CP. WBV therapy has been shown to improve postural control for individuals with multiple sclerosis [52], however, which is another population that commonly experiences spasticity.

Another intervention for improving fall-recovery in children with CP that has shown to be effective in other populations with neuromuscular deficits is perturbation-based fall-recovery training. This type of intervention has been shown to reduce the risk of falling (risk ratio 0.71, 95% CI 0.52 – 0.96) in both older adults and individuals with Parkinson's disease [53]. In addition, a study that implemented repeated slips to individuals with stroke found that the fall-recovery response was modifiable, characterized by a more stable position both before and after a recovery step was taken [54]. Postural control mechanisms have also been demonstrated to be modifiable in

children with CP, where reactive balance training for one week resulted in less sway and a faster time to stabilization after a balance perturbation [55]. While not a specific outcome variable for this study, it was observed that the children with CP were able to "learn" to recover from disturbances during the protocol. An initial belt acceleration of 0.5 m/s^2 caused two of the three participants with CP to fall on their first attempt, yet both were able to recover from the same disturbance without taking a step in the same session.

It is important to note our study limitations. First, outcome variables of dynamic stability and muscle activity were assessed at different perturbation magnitudes. Within each subject, the disturbance magnitude likely influenced these outcomes. In a previous study, typically developing children scaled the amplitude of their neuromuscular response to perturbation magnitude, while children with CP did not [6]. Across subjects in our study, however, we found weak correlations between the muscle activation amplitudes at their respective thresholds and the threshold values themselves, expressed in acceleration or ankle torque ($r = 0.002 – 0.181$). These low correlations suggest that, although we compared different absolute magnitudes of the disturbance, our comparisons represented disturbance magnitudes that were large relevant to the individuals' capabilities. If the same disturbance acceleration was compared across subjects, those individuals who were not challenged may demonstrate a delayed, small muscle response that was sufficient to prevent a step, but at minimal effort.

An additional limitation is that we constrained the stepping response, when that constraint is rarely present in the free-living environment. CP would likely alter the stepping response as well. However, constraints were made to allow for a reliable

measure that could be evaluated by observation alone. In a previous study of 112 older adult women (in prep), single-stepping thresholds were significantly correlated (r = 0.37 - 0.53), with multiple-stepping thresholds, an assessment that allows for a stepping response. Therefore, our evaluation of fall-recovery is likely indicative, in part, of the ability to recover from a fall outside the lab.

3.5 Conclusions

In conclusion, the fall-recovery response in children with CP is impaired based on our objective, quantifiable measure. A compromised ability to recover from dynamic instability was found by clear differences in the MoS achieved between groups. The reason for this deficit may be due to a delayed and insufficient neuromuscular response, which could be a result of abnormal proprioception with spasticity. These abnormalities negatively affect postural control mechanisms that are necessary for effective static and dynamic balance abilities utilized during physical activity. Balance deficits in children with CP are a likely contributor to their decreased physical activity levels, either directly by preventing activity without falls or indirectly by causing fractures and a fear of falling. For this reason, a vital next step in improving the well being of children with CP is exploring interventions that can enable physical activity by improving balance and decreasing fall risk.

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Appendix A

INSTITUTIONAL REVIEW BOARD APPROVAL LETTERS

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: October 23, 2015

TO: Christopher Modlesky
FROM: University of Delaware IRB

STUDY TITLE: [778529-1] Effect of a high-frequency, low-magnitude vibration on the cardiovascular, metabolic and neuromuscular systems and physical activity in children with cerebral palsy: a pilot study

SUBMISSION TYPE: New Project

ACTION: APPROVED
APPROVAL DATE: October 23, 2015
EXPIRATION DATE: July 15, 2016
REVIEW TYPE: Full Committee Review

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document. When consenting please be sure to use a copy of the informed consent document containing the UD IRB Approval Stamp.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: March 20, 2017

TO: Jeremy Crenshaw, PhD
FROM: University of Delaware IRB (HUMANS)

STUDY TITLE: [897744-2] Development of a comprehensive evaluation of postural control in children with cerebral palsy

SUBMISSION TYPE: New Project

ACTION: APPROVED
APPROVAL DATE: March 20, 2017
EXPIRATION DATE: March 14, 2018
REVIEW TYPE: Full Committee Review

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

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Appendix B

PEDIATRIC BALANCE SCALE

APPENDIX

A

PEDIATRIC BALANCE SCALE

Name: _____ Date: _____

Location: _____ Examiner: _____

Item Description		Score *0 - 4*	Seconds *optional*
1.	Sitting to standing	_____	
2.	Standing to sitting	_____	
3.	Transfers	_____	
4.	Standing unsupported	_____	_____
5.	Sitting unsupported	_____	_____
6.	Standing with eyes closed	_____	_____
7.	Standing with feet together	_____	_____
8.	Standing with one foot in front	_____	_____
9.	Standing on one foot	_____	_____
10.	Turning 360 degrees	_____	_____
11.	Turning to look behind	_____	
12.	Retrieving object from floor	_____	
13.	Placing alternate foot on stool	_____	_____
14.	Reaching forward with outstretched arm	_____	
	Total Test Score	_____	

General Instructions

1. Demonstrate each task and give instructions as written. A child may receive a practice trial on each item. If the child is unable to complete the task based on their ability to understand the directions, a second practice trial may be given. Verbal and visual directions may be clarified through the use of physical prompts.

2. Each item should be scored utilizing the 0 to 4 scale. Multiple trials are allowed on many of the items. The child's performance should be scored based upon the lowest criteria, which describes the child's best performance. If on the first trial a child receives the maximal score of 4, additional trials need not be administered. Several items require the child to maintain a given position for a specific time. Progressively, more points are deducted if the time or distance requirements are not met; if the subject's performance warrants supervision; or if the subject touches an external support or receives assistance from the examiner. Subjects should understand that they must maintain their balance while attempting the tasks. The choice, of which leg stand on or how far to reach, is left to the subject. Poor judgement will adversely influence the performance and the scoring. In addition to scoring items 4, 5, 6, 7, 8, 9, 10, and 13, the examiner may choose to record the exact time in seconds.

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