SENSORIMOTOR CONTROL OF WALKING BALANCE IN INDIVIDUALS WITH AND WITHOUT CEREBRAL PALSY

by

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A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

Summer 2023

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ACKNOWLEDGMENTS

To my primary adviser, Dr. Samuel Lee. Thank you for giving me the autonomy and the support to pursue my own independent research project, for always treating me as an equal, and for not just being a great mentor but, more importantly, for also being a great person to work with.

To my co-adviser, Dr. John Jeka. Thank you for "adopting" me into the CoBaL team and for helping me pursue a project that was truly interdisciplinary, and for your continued mentorship and encouragement in navigating the big bad world of academia.

To my dissertation committee: Dr. Hendrik Reimann, this dissertation would not have been possible without your mentorship. I am grateful for all that you have taught me with so much patience and humility. Thank you for shaping me into the researcher I am today. Jeremy Crenshaw, you have been involved in my dissertation right from my first semester at UD and have always had feedback that has only made my work better. Dr. Laura Prosser, thank you for your time and effort, and for your clinical expertise on this project.

To my fellow lab mates from both the Pediatric Mobility Lab and the CoBaL lab, Khushboo Verma, Stephen diBianca, Julia Gray, Felipe Yamaguchi, and Eman Alsaqabi, thank you for making work fun. A special thank you to Maelyn Arcodia for helping me with my data collections and sacrificing your weekends for the sake of science. I am truly grateful for our friendship. To my predecessor, Dr. Ahad Behboodi, thank you for being a great sounding board, friend, collaborator and for blazing a trail!

To Henry Wright, thank you for helping me with the FES project, and to Jaime Alesi, for helping me with building the SR system, the software setup and coding.

Last but certainly not least, I would like to thank my family and friends: To my parents, who sent me to the United States a decade ago with a large portion of their lives' savings so I could go to a PT school here. I owe all the opportunities that came my way after coming to this country, right up to the completion of this degree, to your sacrifices and to your absolute faith in me. To my sister, Sameera, for being someone I can always count on. Finally, thank you to my husband, Manish, for being my biggest champion, loudest cheerleader, for giving me a shoulder, a hand and a push when needed, and, above all, for being my home.

FUNDING SOURCES

This work has been made possible through the generous support of the following funding sources: the University of Delaware through the Unidel Distinguished Graduate Scholars Award; the Foundation for Physical Therapy Research through their Promotion of Doctoral Studies II Scholarship; as well as grant support from the American Society of Biomechanics Grant-In-Aid.

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ABSTRACT

Individuals with cerebral palsy (CP) are at a high risk of falling, with about 35% reporting daily falls. Falls can occur because of problems in either sensing the motion of the body in space, or in generating an appropriate motor response to the perceived motion. Individuals with CP have well-documented deficits in processing and integrating sensory input, which can play a significant role in balance control. However, the current standard of care for balance problems in CP largely focuses on motor deficits, with limited consideration of sensory impairments. Thus, there is a critical need to investigate the role of sensory processing in balance control in individuals with CP. The overarching goal of this dissertation was to investigate how individuals with CP use sensory information, particularly vision, to control walking balance and whether augmenting their sensory input, specifically, proprioception, can improve their walking balance.

Proprioceptive deficits in individuals with CP are associated with higher reliance on visual feedback to control standing balance. It is not well understood how individuals with CP use visual information for sensorimotor feedback control of balance during walking. In Aim 1, we used visual perturbations to understand how individuals with and without CP integrate visual input for walking balance control. We found that compared to their typically developing (TD) peers, the overall body sway in response to the visual perturbations was magnified and delayed in CP group, implying that they were more affected by changes in visual cues and relied more so on visual information for walking balance control. Also, the CP group showed a dominant

proximal foot placement strategy and diminished ankle roll response, suggestive of a reliance on proximal over distal control of walking balance in individuals with CP.

In Aim 2, we investigated the immediate effects of augmenting proprioception through the application of a sensory-centric intervention, such as stochastic resonance (SR) stimulation, on walking balance in individuals with CP and TD. We found that SR application resulted in a small but significant increase in lateral and anterior margin of stability. This implies that with SR, a larger impulse was needed to become unstable. This suggests that SR stimulation, which is known to enhance proprioception, may have improved the CP group's awareness of body motion during walking.

Lastly, it is not known if visual reliance can be reduced by providing SR stimulation to increase the acuity of proprioceptive feedback. Thus, by upweighting the proprioceptive input, SR can potentially reduce the reliance on visual input for balance control, freeing visual information for high-level tasks like navigation and obstacle avoidance. In Aim 3, we investigated if SR stimulation results in reduced reliance on vision during visually perturbed walking in individuals with CP and TD. We found that the response to visual perturbations was significantly smaller with SR in the CP group, while the TD group did not show any significant change with versus without SR. We propose that SR, by enhancing proprioception, may have led to upweighting of proprioception and downweighing of visual input, leading to a reduced reliance on vision for walking balance control.

Overall, the findings from this dissertation will aid in development of a sensory-based treatment approach and will be a critical addition to the current motor-centric treatments, thus providing a more comprehensive approach to balance rehabilitation in CP.

Chapter 1

INTRODUCTION

1.1 Balance Control in Cerebral Palsy.

Nearly 1 in every 500 children has an injury to the developing fetal or infant brain, which affects the development of posture and movement, leading to cerebral palsy (CP).[1] Postural instability is the most significant contributor to the primary impairments in CP compared to motor deficits such as abnormal muscle tone and coordination.[2] Among those children with CP classified as ambulatory with low function (i.e. Gross Motor Functional Classification System Levels-GMFCS level II), more than half report falling at least daily, whereas for those with higher motor function (GMFCS level I), about a third report falling at least once a week.[3] These falls not only lead to serious injuries to the head, spine and limbs, but also affect psycho-social health, resulting in fear, embarrassment and the feeling of powerlessness.[4] Therefore, addressing postural instability and enhancing balance control during walking in children with CP is critical for reducing fall risk and fall-related sequelae.

1.2 Sensory deficits in CP

Control of balance during walking requires contributions from motor as well as sensory systems. Falls can occur due to either deficits in sensory systems, i.e., inability to quickly sense the movement of the body in space, or deficits in motor systems, i.e., failure in generating appropriate motor response. Sensory processing deficits in CP have been implicated through numerous neuroimaging studies showing disrupted thalamocortical pathways and aberrant somatosensory cortical activation.[5–8] Abnormal somatosensory cortical activity in individuals with CP was observed during the motor planning and movement execution, implying deficits in the anticipatory feedforward mechanisms.[6] Additionally, abnormal somatosensory cortical activity was associated with increased errors in attaining the target force production during a goal oriented task, implying impaired sensorimotor integration and feedback mechanisms in CP.[9] Altogether, these findings suggest that sensory processing deficits in CP can affect the ability to not only plan and execute a motor task, but also to correct errors in motor performance and adapt to a changing environment, both of which are extremely critical in balance control during a dynamic activity such as walking.

1.3 Link between sensory deficits and balance control in CP

There is increasing evidence that links sensory deficits, both central and peripheral, to balance control and walking performance in CP. Mobility impairments in CP, including slower walking speed and shorter steps have been associated with abnormal somatosensory cortical activity.[9] Additionally, poor performance on clinical sensory tests of lower extremity, such as aberrant two-point discrimination, light touch, hip and ankle joint position sense have been found to have moderate to strong relationships with reduced balance parameters such as increased postural sway, poor BESTest scores and with reduced walking performance such as slower gait speed, shorter step length, shorter 6MWT distance.[10,11] In summary, these findings suggest a strong link between somatosensory deficits and postural control in CP possibly by affecting sensory feedback during the execution of a motor response, or by altered development of the desired motor plan.

Despite such compelling evidence that supports the role of sensory processing as a key component in maintaining balance control during walking, there is a lack of research that investigates how sensory input affects balance control in individuals with CP. Further, effective interventions that include sensory facilitation as a part of rehabilitation protocols are limited. The overarching goal of this dissertation was to probe the role of sensory processing in individuals with CP and to provide preliminary evidence for the use of a sensory-centric modality in improving walking balance in CP.

1.4 Overall Scientific Premise

1.4.1 Scientific Premise for Aim 1

Individuals with CP compensate for sensory processing deficits by depending on visual information over other sensory modalities for regulating upright posture. Increased visual dependency is associated with abnormal balance strategies in CP[12] and with increased fall risk during walking.[13–15] While increased dependency on visual information over proprioception in children with CP was established in single plane upper and lower extremity movements[16] and during standing[17], the implications for balance control during walking have so far not been studied. Disrupted visual feedback during walking resulted in amplified COM motion and increased step-to-step variability in older adults, a population known to have reduced somatosensory feedback.[18] However, whether these results can be extended to individuals with CP is yet to be determined.

Knowledge gap: It is not known if individuals with CP show increased reliance on visual feedback to control balance during walking as compared to TD peers.

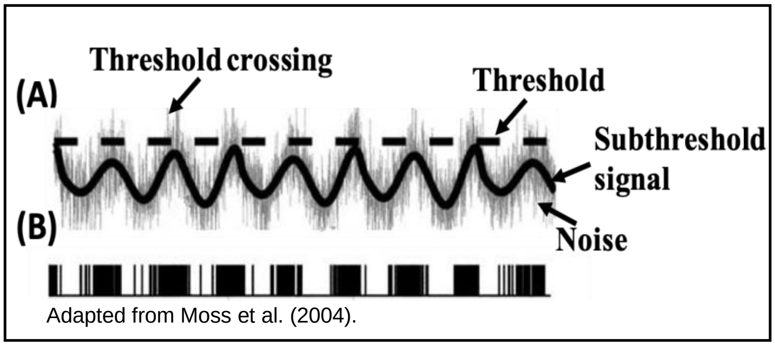
The primary purpose of Aim 1 was to investigate whether individuals with and without CP show increased reliance on visual input through increased medio-lateral center of mass excursion to control their balance while walking.

1.4.2 Scientific Premise for Aim 2

There is a lack of effective interventions that include sensory facilitation as a part of rehabilitation protocols. While a variety of therapeutic interventions have addressed musculoskeletal deficits such as muscle weakness, spasticity, poor flexibility, and contractures, with mixed or unsuccessful outcomes,[19–22] there is limited consideration of sensory impairments. There are currently no interventions that specifically augment sensory feedback and address sensory regulation of gait in CP. The possibility of reversing somatosensory deficits with targeted sensory therapy has been demonstrated through a randomized control trial on adults with CP, which showed improvement in pain thresholds after somatosensory therapy,[23] as well as a neuroimaging study, which demonstrated the plasticity of white matter tracts after physical therapy and botox injections.[24] Thus, there is a potential to improve sensory regulation of balance control with a sensory-centric modality that can augment proprioceptive feedback while walking.

In this proposal, we address the need for sensory regulation through application of a novel, sensory-based modality called stochastic resonance stimulation (SR). SR is a phenomenon where random, sub-sensory noise improves the sensitivity of a sensory system to detect a weak signal. This phenomenon has been observed in various biological systems.[25] The neurophysiological mechanism behind this phenomenon is that the subthreshold electrical noise signals cause small changes in the transmembrane potentials of proprioceptive receptors, making the sensory neuron more likely to fire an action potential in the presence of a weak stimulus (Figure 1.1).[26–28]

Figure 1.1: Top panel (A) depicts a subthreshold signal (thick black line) that crosses the threshold (dashed black line) after addition of noise (gray). Bottom panel (B) depicts the action potentials fired at threshold crossings, leading to spike trains.



Application of SR has resulted in significantly improved standing balance in patients with functional ankle instability (FAI),[29,30] diabetic neuropathy,[31] stroke,[31] and older adults.[31,32] Specifically with respect to walking, older adults and frequent fallers have shown reduced variability in their spatio-temporal gait parameters after SR stimulation, which is indicative of improved regularity and rhythmicity of gait.[33,34]

Despite such substantial results with SR stimulation in populations with proprioceptive deficits, its use for improving walking balance control in a neurodevelopmental disorder such as CP is novel. One critical component of SR stimulation is ensuring delivery of appropriate level of SR intensity. SR intensities that are too low or too high can have detrimental effects on detection of the proprioceptive signal.[27,30,35] Hence, customizing the SR intensity to each individual is critical for maximizing balance improvements. A prior study that explored the effects of SR stimulation combined with perceptual-motor intervention on seated postural stability in children with CP aged 2-6 years showed that SR did not improve sitting behavior.[36] However, the authors determined the intensity of SR stimulation based on facial expressions of the children, possibly resulting in inappropriate stimulation levels. Additionally, SR stimulation was applied via the seating surface and not directly to the trunk whose musculature would provide postural corrections. We have addressed the problem faced in the above study in a recently published work by our group on effects of SR stimulation on standing balance in children with CP.[11] We applied SR stimulation to the ankle ligaments and leg musculature of children with CP using an optimization protocol to ensure appropriate levels of subject-specific SR stimulation were delivered.[30] Our results show that SR stimulation significantly improved the postural sway of children with CP compared to no stimulation condition in standing. However, it is yet to be determined if these results can transfer over to walking, which is inherently a more complex and unstable activity. The configuration of the body during walking changes substantially between different phases of the gait cycle, e.g. double vs. single stance, requiring different biomechanical mechanisms to maintain upright balance at different points of the cycle.[37] More importantly, about 55% of the falls in individuals with CP occur in walking and an additional 39% occur during walking related activities such as turning, bending and lifting.[4] Thus, it is critical to investigate if the improvements in balance obtained in our standing study transfer over to walking. The overall goal of our proposal is to investigate if a sensory-based modality such as SR can augment sensory feedback and improve balance control during walking. Aim 2 will investigate the immediate effects of SR stimulation on balance control through margin of stability during unperturbed walking in children with CP as compared to children with typical development (TD).

Knowledge gap: There is a lack of a therapeutic intervention addressing sensory function during walking to enhance balance control in children with CP.

Aim 2 will investigate the immediate effects of SR stimulation on balance control through margin of stability during unperturbed walking in children with CP as compared to children with typical development (TD).

1.4.3 Scientific Premise for Aim 3

The central nervous system adapts to changes in the environment by continuously adjusting the relative weight of different sensory sources such as vision, proprioception, and vestibular system i.e., "sensory reweighing" (Peterka, 2002). Thus, more reliable sensory input is weighed more strongly than the less reliable input. The ability to upweight (i.e., increase the reliance on) the proprioceptive input as needed, especially in situations where one might receive insufficient or conflicting visual input e.g., moving from a well-lit to a dark room, is extremely important in maintaining upright balance. Sensory augmentation feedback through vibrotactile cues has reduced the COM displacement after translational perturbations in standing in healthy young adults.[38] In the pediatric population, children with TD can reweight multisensory inputs from visual and proprioceptive sources from 4 years of age onwards.[39] Thus, they could reduce the reliance on vision when subject to visual perturbations of increasing amplitude in standing and could reduce reliance on tactile input when the amplitude of the contact surface perturbation was increased. It is not known if children with CP will be able to upweight proprioceptive feedback and show reduced visual dependence if they receive a sensory-centric modality that augments the detectability of proprioceptive signal.

Knowledge gap: The increased dependency on visual information in CP is not addressed in current therapeutic approaches.

By upweighting proprioceptive input, this modality may reduce the dependence on visual input for balance control, freeing visual information for high-level use like navigation and obstacle avoidance. This project proposes to address the visual reliance in CP during walking by using SR to increase the acuity of proprioceptive feedback.

Aim 3 of this study is to test whether SR stimulation reduces the reliance on vision by decreasing medio-lateral center of mass excursion in children with CP compared to TD during visually perturbed walking.

1.5 Innovation

The work proposed here contains four major areas of innovation over existing approaches:

1. We address the sensory processing aspect of the balance problem using Stochastic Resonance stimulation. The present work explores an area of research that has only recently begun to gain attention, i.e., investigation of somatosensory processing in children with CP. Little focus has been placed on understanding the sensory feedback deficits in CP and how they influence motor control. While problems with postural control are associated with deficits in sensory processing in children with CP,[10,11] no previous work has addressed the sensory regulation of walking balance in children with cerebral palsy. This work provides an innovative departure from the current standard of care by developing a modality to address these issues with the sensory side of the sensorimotor control loop with Stochastic Resonance (SR) stimulation.

2. We assess balance control during walking, instead of standing. Upright balance has been studied largely during standing,[40] using a variety of techniques with quiet, unperturbed stance as well as sensory and mechanical perturbations.[41,42] However, these findings do not easily translate or apply to balance control during walking. Additionally, most falls in children with CP occur while walking, not standing.[4] Here we study walking directly, in a laboratory setting containing similar movement and sensory processing requirements as walking in the community and other activities, where falls actually occur.

3. We investigate if somatosensory upweighting can be achieved to improve balance during walking. The increased dependency on visual information over proprioception in children with CP was established in single plane movements[16] and during standing,[17] but the implications for balance control during walking have so far not been studied. Additionally, it is not known if a sensory-centric modality can upweight somatosensory input and improve control of balance. This work helps to fill this gap by using a virtual reality environment to probe the link between increased visual dependency and balance control during walking in children with CP. Furthermore, using visual perturbations allows us to directly disrupt the sensory mode that children with CP tend to rely most on for balance control, probing whether SR can address the specific sensory problems they experience.

4. We apply stimulation at hip and ankle joints, instead of only at the ankle. SR stimulation to improve balance control in standing is usually applied at the ankle joint.[30,43] In quiet standing, movement around the ankle joint has the largest effect on body sway,[44] so improving proprioceptive information is most beneficial at the muscles and ligaments surrounding this joint, although Gravelle et al[32] have shown

that SR stimulation at the knee led to reduced postural sway during standing. In walking, the hip joint is critical for lateral balance. It transitions from almost free movement during swing to stabilization and weight-bearing of the majority of the body weight during stance. Experimentally altering proprioceptive signals at the hip joint using vibration led to changes in foot placement for balance control in healthy young adults.[45] We account for the role of the hip joint during walking by applying SR stimulation at the ankle and hip joints of both legs during walking.

1.6 Specific Aims

Aim 1: Investigate how individuals with CP use visual input for walking balance control compared to those with typical development (TD) in response to visual perturbations. I will use a virtual reality environment to provide a visual fall stimulus and measure the resulting shift of center of mass (COM).

Hypothesis 1: Individuals with CP will demonstrate significantly increased medio-lateral (M-L) COM excursion than their TD peers.

Aim 2: Investigate the immediate effects of SR stimulation on balance control during unperturbed walking through margin of stability in individuals with CP as compared to individuals with TD.

Hypothesis 2: SR stimulation during walking will enhance balance control through increased margin of stability, with greater improvements in the CP group compared to the TD group.

Aim 3: Investigate whether SR stimulation, through improved proprioception, reduces responses to visual fall perturbations by decreased M-L COM excursion during walking in children with CP and TD.

Hypothesis 3: SR stimulation will reduce the responses to visual perturbations through decreased M-L COM excursion compared to no SR, with greater reduction in the CP compared to TD.

Chapter 2

INDIVIDUALS WITH CEREBRAL PALSY SHOW ALTERED RESPONSES TO VISUAL PERTURBATIONS DURING WALKING

2.1 Preface

At the time of publication of this dissertation, the following chapter has been published and reflects Aim 1 of this dissertation. This article was published in Frontiers in Human Neuroscience.[46]

Sansare A, Arcodia M, Lee SCK, Jeka J, Reimann H. Individuals with cerebral palsy show altered responses to visual perturbations during walking. Front Hum Neurosci. 2022 Sep 8;16:977032. doi: 10.3389/fnhum.2022.977032. PMID: 36158616; PMCID: PMC9493200.

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2.2 Abstract

Individuals with cerebral palsy (CP) have deficits in processing of somatosensory and proprioceptive information. To compensate for these deficits, they tend to rely on vision over proprioception in single plane upper and lower limb movements and in standing. It is not known whether this also applies to walking, an activity where the threat to balance is higher. Through this study, we used visual perturbations to understand how individuals with and without CP integrate visual

input for walking balance control. Additionally, we probed the balance mechanisms driving the responses to the visual perturbations. More specifically, we investigated differences in the use of ankle roll response i.e., the use of ankle inversion, and the foot placement response, i.e., stepping in the direction of perceived fall. Thirty-four participants (17 CP, 17 age-and sex-matched typically developing controls or TD) were recruited. Participants walked on a self-paced treadmill in a virtual reality environment. Intermittently, the virtual scene was rotated in the frontal plane to induce the sensation of a sideways fall. Our results showed that compared to their TD peers, the overall body sway in response to the visual perturbations was magnified and delayed in CP group, implying that they were more affected by changes in visual cues and relied more so on visual information for walking balance control. Also, the CP group showed a lack of ankle response, through a significantly reduced ankle inversion on the affected side compared to the TD group. The CP group showed a higher foot placement response compared to the TD group immediately following the visual perturbations. Thus, individuals with CP showed a dominant proximal foot placement strategy and diminished ankle roll response, suggestive of a reliance on proximal over distal control of walking balance in individuals with CP.

2.3 Introduction

Individuals with cerebral palsy (CP) are at a high risk for falls, with about 35% reporting daily falls and 30% reporting weekly or monthly falls [3]. These falls not only lead to serious injuries to the head, spine, and limbs, but also affect psycho-social health, resulting in fear, embarrassment, and the feeling of powerlessness in individuals with CP [4]. To maintain upright balance, the nervous system uses sensory information to determine how the body moves through space and generates appropriate motor command to modulate that movement and keep the body upright. Thus, both sensory and motor deficits can impair the functioning of this sensorimotor control loop and contribute to balance problems and fall risk. Rehabilitation approaches generally focus on the motor aspect of balance control, and most studies in CP examine the postural control strategies due to altered muscle recruitment strategies [47] and kinetics [48], often using mechanical perturbations [49,50]. However, the effect of sensory deficits on sensorimotor control of balance in walking is currently not well understood.

Individuals with CP have deficits in processing of somatosensory and proprioceptive information. CP is associated with altered sensorimotor cortical activation and disrupted sensory white matter connections [6,8,9] and poor performance on clinical sensory tests, such as reduced scores in two-point discrimination, light touch, and hip and ankle joint position sense [10,11]. There is increasing evidence that these sensory deficits are linked to deficits in balance control and walking performance in CP. Mobility impairments in CP, including slower walking speed and shorter steps, are associated with abnormal somatosensory cortical activity [9]. Additionally, poor performance on clinical sensory tests at the legs, such as impaired two-point discrimination, light touch, hip, and ankle joint position sense, have moderate to strong relationships with reduced balance parameters such as increased postural sway, poor scores in the Balance Evaluation Systems Test (BESTest), as well as with reduced walking performance such as slower gait speed, shorter step length, shorter 6 Minute Walk test distance [10,11]. These findings suggest a causal link of deficits in somatosensory and proprioceptive processing and to impairments in postural control in CP.

Individuals with CP use visual information to compensate for deficits in somatosensory and proprioceptive processing. Occluded vision results in higher errors during single plane upper and lower extremity movements in individuals with CP [16]. Individuals with CP exhibit larger and more variable body sway in maintaining upright stance in response to visual manipulation of the surrounding environment than typically developing peers [17,51]. Removal of visual input worsens the crouch stance by increasing hip-knee flexion in individuals with CP, suggesting that visual input is important for maintaining standing posture in individuals with CP[52]. The degree of visual dependency during standing is associated with abnormal balance strategies in CP [12] and an increased risk of impaired development in posture, spatial awareness, and movement skills [53]. Visual dependency is associated with poor balance and increased fall risk in older adults and people with vestibular disorders [13–15], suggesting that vision can only compensate for deficits in other sensory modalities to a certain degree.

While increased reliance on visual information over proprioception in individuals with CP was established in single plane upper and lower extremity movements [16] and during standing[17], the implications for balance control during walking have so far not been studied. Though it is reasonable to assume that sensory integration is similar between standing and walking, the effect of visual dependency on balance in walking has not been studied in individuals with CP. The biomechanics of the walking human body are substantially more complex than in standing. The body configuration changes substantially during the gait cycle, requiring different biomechanical mechanisms to modulate body movement and maintain upright balance (22). Due to this biomechanical difference, it is unclear if results from studies on sensory processing for balance in standing will translate to walking. Moreover, the majority of falls in individuals with CP occur in walking and other dynamic activities such as turning, bending, and lifting [4], rather than in standing. Hence it is critical to investigate how the visual dependency seen in standing balance affects balance control during walking in individuals with CP.

A typical response to a visual fall stimulus is to move the center of mass (CoM) away from the direction of the fall. People react to a leftward fall stimulus by moving their body to the right. Visual perturbations during walking in older adults resulted in increased CoM motions, implying that aging induced degradations in proprioception may lead to reliance on visual feedback [18]. Our hypothesis that individuals with CP compensate for proprioceptive deficits by relying more on visual information predicts that responses to visual fall stimuli during walking will be larger in individuals with CP, because they rely more on visual feedback than on the proprioceptive or vestibular information indicating that the body is not actually falling. The CoM response to visual fall stimuli is generated by two different biomechanical mechanisms in healthy adults. Immediately following a fall stimulus, they change the foot placement location of the next step in the direction of the perceived fall, which changes the lever arm of the gravitational force and accelerates the body in the opposite direction[54]. This is known as the "foot placement mechanism" for balance control [55,56]. The second mechanism is to use lateral ankle musculature during single stance to actively pull the body to the side [37,57], referred to as "ankle roll mechanism." The ankle roll mechanism is important for balance control in walking. Although it is limited in extent by the contact area under the stance foot and usually small, it can often be applied earlier than the foot placement mechanism, which is limited by the step time. Modelling results [58] indicate that in the absence of ankle response, a larger foot placement response is needed to upright balance. In standing balance control, individuals with CP tend to favor responses with the hip joints over ankle joint responses, activating the proximal musculature around the hips rather than showing the distal-to-proximal strategy usually observed in neurotypical adults [48,59]. We hypothesize that individuals with CP show a similar preference of proximal over distal responses in walking balance control, predicting that they will show reduced response in the ankle roll mechanism and increased response in the foot placement mechanism. In this study, we investigated how individuals with CP integrate visual information for walking balance control by inducing visual fall stimuli in a virtual reality environment in individuals with and without CP. We measure the overall CoM response to the fall stimuli, and the responses in the foot placement and ankle roll balance mechanisms that generate the CoM movement. We hypothesize that people with CP compensate for proprioceptive and somatosensory deficits by relying more on visual information for balance and that they will favor proximal over distal mechanisms to control body movement. These hypotheses predict that individuals with CP (i) will display a larger

CoM response to visual perturbations and (ii) will show larger foot placement response and reduced ankle roll response than age- and sex-matched peers.

2.4 Methods

2.4.1 Participants

Seventeen ambulatory individuals and adolescents with spastic diplegic or hemiplegic CP were recruited through the CP clinic at local hospitals. We specifically recruited individuals with Gross Motor Function Classification System (GMFCS) levels I-II [60] so that they would be able to complete our visual perturbation paradigm without relying on a handrail for tactile or visual cues. Seventeen typically developing (TD) individuals, who were age-matched (± 6 months) and sex-matched with the CP group, were recruited through flyers, local advertisements, and social media. The protocol was approved by the University of Delaware Institutional Review Board, and informed parental consent and assent were obtained. All participants were screened by a physical therapist for the inclusion and exclusion criteria (Table 2.1). Of note, we only included individuals with normal or corrected to normal vision (such as with glasses or contact lenses) and excluded any individuals with any ocular impairments as well as known diagnosis of cerebral visual impairment (CVI). Additionally, all of our patients had at least 5 degrees of active motion in plantarflexion and dorsiflexion, at least 10 degrees of active knee flexion and at least 10 degrees of active hip flexion and extension. To analyze effects of laterality, we determined the *more affected side* as the one with hemiplegia in individuals with hemiplegic CP, the one self-identified as the more affected side in individuals with diplegic CP, and the non-dominant side for individuals with TD. The dominant side in the TD group was self-determined by the participants as their preferred lower limb of use during daily activities.

Table 2.1. Inclusion and exclusion criteria. * denotes criteria applicable to TD group

Inclusion	Exclusion
• Age 8 - 24 years • Diagnosis of spastic diplegic or hemiplegic CP • GMFCS classification level I or II (ability to walk independently with using any assistive device) • Visual, perceptual, and cognitive/ communication skills to follow multiple step commands • Seizure-free or well controlled seizures • Ability to communicate pain or discomfort during testing procedures • Parental/guardian consent and child assent/consent	• Diagnosis of athetoid, ataxic or quadriplegic CP • Significant scoliosis (scoliometer angle > 9°) • History of selective dorsal root rhizotomy • Botox injections in the lower limb within the past 6 months • Severe spasticity of the lower extremity muscles (e.g., a score of 4 on the Modified Ashworth Scale) • Severely limited range of motion/ irreversible muscle contractures • Lower extremity surgery or fractures in the year prior testing* • Joint instability or dislocation in the lower extremities* • Marked visual or hearing deficits*

2.4.2 Instrumentation

All participants walked on a split-belt treadmill (Bertec Inc., Columbus, Ohio, USA) within a virtual reality environment projected on a domed screen covering the participant's complete field of vision. The virtual scene consisted of floating cubes that formed a 4-m wide, infinitely long corridor along a checkered floor (Unity3d, Unity Technologies, San Francisco, CA, USA). The treadmill was self-paced using a custom Labview program (National Instruments Inc., Austin, TX, USA), with the speed of the treadmill adapting in real time to the participant's self-selected speed by keeping the midpoint between the posterior superior iliac spine markers in the anterior-posterior center of the treadmill. Additionally, the perspective in the virtual world was linked to the markers on the forehead and adapted in real time to the participant's head movement. Figure 2.1 shows the virtual reality cave and the virtual scene used in this experimental protocol. These features created a compelling and immersive virtual reality experience similar to what one would experience when walking over-ground. Participants were in a safety harness at all times that protected them against falls but did not provide support during normal walking. To induce visual perturbations, the virtual scene was rotated around the central anterior-posterior axis of the treadmill with an angular acceleration of $45°/s^2$ for 600 ms, starting at heel-strike of either foot, then remained tilted for 2000 ms and was reset to the horizontal axis over the next 1000 ms with constant angular velocity. This rotation generates optical flow on the participant's retina that is similar to the optical flow of falling sideways around the stance foot contact point. These perturbations were triggered at pseudo-randomly selected heel strikes of either foot. Each such trigger was followed by a 10-12 step washout period between the reset of the visual scene and the next trigger. To determine the effect of the visual stimulus relative to unperturbed walking, we alternated between periods of actual and sham stimulation. The average walking pattern of the sham stimulation periods was used as control for each participant. A sham stimulation was a period of 10-12 steps where the participant would not receive any visual perturbation. i.e., they continued walking in an unperturbed manner for these steps. We have used this visual stimulation paradigm extensively in our previous work [37,54,61].

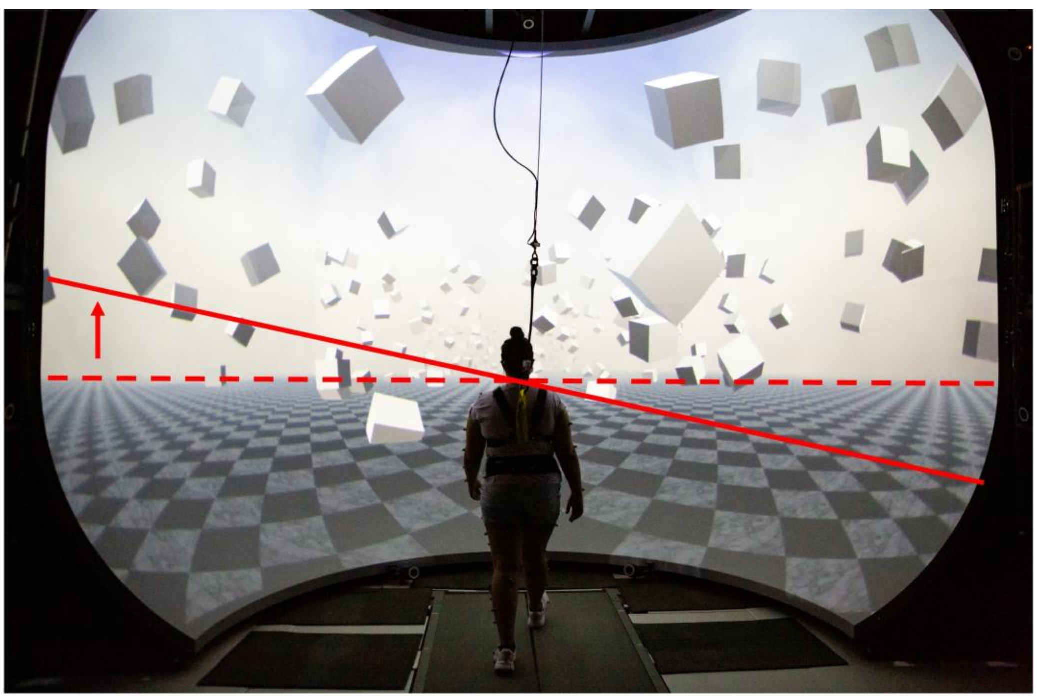

Figure 2.1: Virtual Reality Environment. The solid red line shows the tilt of the horizon (dashed) during the visual fall for a left sided virtual fall. Similar degree of tilt on the opposite side was generated for a right sided fall.

2.4.3 Protocol

Each participant was given at least two 2-minute practice trials to get accustomed to the self-paced treadmill and the virtual environment, one trial without visual perturbations, and another practice trial with visual perturbations. Before beginning the practice walking trial with visual perturbations, the participants were given a demonstration of the visual perturbations to each side while in standing. We asked participants if they felt comfortable with the system after these two practice trials and offered additional practice on request.

After completing the practice phase, participants performed ten 2-minute walking trials, with a 15 second ramp-up period prior to the start of the 2 minutes to reach steady-state walking. Participants received visual fall stimuli as described above during the 2-minute period. After each trial, the treadmill was stopped, and participants were offered a rest break.

2.4.4 Data Analysis

Full body kinematics were measured using a 13-camera motion capture system (Qualysis Inc., Gothenberg, Sweden) and a full body Plug-in Gait marker set[62] with six additional markers on anterior thigh, anterior tibia, and 5th metatarsal head bilaterally. For the static calibration pose at the beginning of the collection, an additional six markers were placed on bilateral medial femoral epicondyles, medial malleoli, and the tip of the first distal phalanx of the foot. Heel strikes were tracked using the position of marker on the heel of each foot and were defined as the maxima of the anterior-posterior position of the heel-marker. We recorded electromyography (EMG) signals from peroneus longus, using Cometa's PicoEMG sensors (Bareggio, Italy) with hydrogel 30 × 24 mm Covidien Kendall electrodes with SENIAM guidelines for placement. To normalize EMG, we divided by the average signal for each muscle across all the control steps. Marker data were recorded at 200 Hz, EMG at 2000 Hz and ground reaction forces and moments at 1000 Hz. Force plate data was low pass filtered with a 4th order Butterworth filter at a cut-off frequency of 20 Hz. EMG data was rectified, then low pass filtered with a 4th order Butterworth filter at a cut-off frequency of 6 Hz. Inverse kinematics for a 15-segment biomechanical model were computed using OpenSim 4.0 [63]. The data was further processed using custom scripts in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States). We analyzed the first eight steps following a visual stimulus. All data was time-normalized to 100 time points per step. For visual presentation in the figures, we scaled the normalized time to the average step time for each step. For all trajectories, the mean of control data for the same stance foot was subtracted from the stimulus data to estimate the response due to the visual stimulus. For spatial variables, the data from stimuli triggered by a left heel strike were inverted for body symmetry, such that positive values refer to the direction *towards the leg that triggered the stimulus* and negative refers to the direction *away from the leg that triggered the stimulus*. We determined heel strike and push off events as the maxima and minima of the heel marker relative to the midpoint of the pelvis markers in anterior-posterior direction.

2.4.5 Outcome Measures

The primary outcome measure to quantify the overall response to visual perturbations was the area under the curve (AUC) of the medio-lateral CoM excursion. We defined the CoM excursion as the difference between the average CoM for the perturbed steps from control for each participant and integrate over the eight steps following the heel strike that triggered a stimulus. We also determined the peak of the CoM excursion over the same period and used the magnitude of the peak to quantify the extent and the delay between the peak and the triggering heel strike to quantify the timing of the response.

To quantify the ankle roll, we calculated the subtalar angle and the peroneus longus EMG at the stance leg, integrated over the first single-stance period following perturbation onset.

To quantify the foot placement response, we first accounted for the normal variations of the foot placement based on the kinematics of the CoM. We fitted a linear model with the position and velocity of the CoM relative to the stance foot ankle at midstance as predictor and the medial-lateral foot placement as outcome to the data from all control steps for each participant[55]. To estimate the change in foot placement induced by the visual stimulus, we used this linear model to predict the foot placement location from the preceding CoM state, and then subtracted this prediction from the observed foot placement location [45,58]. In addition to the foot placement change at the first post-perturbation step, we also calculated the average foot placement response over the first three post-perturbation steps as a measure of the overall foot placement response, because we expected a delayed response in individuals with CP. These outcome measures have been previously used to assess balance response to visual perturbations [54,64,65].

In addition to these primary outcome measures, we also calculated body-mass index (BMI), and the average cadence, step length, step width, step time and velocity. Step time is the time between consecutive heel strikes, cadence the inverse of the step time, step length and width the difference between the locations of the ankle markers at consecutive heel-strikes and velocity is step length divided by step time.

2.4.6 Statistical Analysis

Data were analyzed using separate two-way mixed ANOVAs, with group (CP, TD) as the between subject factor and side (more affected, less affected) as the within-subject factor. We expected a group by side interaction where participants with CP would perform worse on the affected side when compared to their TD counterparts. We assessed assumptions of homoscedasticity and normality, respectively, by Levene's and Shapiro-Wilk tests in addition to visual examination. Between group differences for baseline characteristics such as age, body mass index (BMI), cadence, velocity, step length, step time and step width were assessed using paired samples t test.

2.5 Results

All participants responded to the visual fall stimuli without having to use the safety harness or stepping off the treadmill.

Most participants (31 out of 34) responded to the visual perturbations by moving their CoM away from the direction of virtual fall, as expected. Two participants from the CP group responded to the fall stimulus by moving their CoM in the opposite direction, towards the perceived fall rather than away from it. One participant from the CP group responded by lunging forward and crouching instead of moving in the mediolateral direction. We chose to exclude these three participants and their respective controls from the statistical analysis, because the CoM response of these three participants was atypical and not representative of the remaining participants in their cohort, so that averaging across the whole group would distort the results and not be representative of the group-wide behavior. Data from these individuals is included in the supplementary material (Figure 2.10). Additionally, EMG data from two participants from the TD group and one participant from the CP group were excluded from the analysis due to technical issues during the data collection. The final number of participants analyzed was 14 CP and `14 TD, with the exception of the peroneal EMG analysis, which included data from 13 CP and 12 TD.

The demographic and spatiotemporal gait parameters for both groups are reported in Table 2.2. The BMI of the CP group was significantly lower than that of the TD group. Additionally, their cadence was significantly higher, and step length and step time significantly lower than that of the TD group. No significant between-group differences were found for age, velocity, and step width. Out of the fourteen individuals in the CP group, there were four participants with hemiplegia and the remaining ten had diplegia.

Table 2.2: Mean, standard deviation (SD) and p values for the difference between the CP and TD groups for demographic and spatiotemporal gait variables.

	CP (n=14)	TD (n=14)	
	Mean ± SD	Mean ± SD	p value
Age	16.3 ± 4.3	16.1 ± 4.2	0.27
BMI	19.0 ± 3.1	23.6 ± 4.7	0.011
Cadence (steps/min)	115 ± 10	106 ± 9	0.007
Velocity (m/sec)	0.966 ± 0.186	1.026 ± 0.166	0.277
Step Width (m)	0.159 ± 0.065	0.124 ± 0.034	0.091
Step Length: More affected side (m)	0.502 ± 0.087	0.577 ± 0.075	0.012
Step Length: Less affected side (m)	0.501 ± 0.087	0.579 ± 0.072	0.008
Step Time: More affected side (sec)	0.528 ± 0.047	0.572 ± 0.051	0.01
Step Time: Less affected side (sec)	0.528 ± 0.047	0.570 ± 0.050	0.007

2.5.1 Center of Mass response

Table 2.3 presents the descriptive statistics for all outcome variables, separated by factors group and side. Figure 2.2 shows the average ML CoM excursion over eight post-perturbation steps. Visual perturbations resulted in an overall larger CoM excursion in individuals with CP. Figure 2.3 shows box and whisker plots for AUC CoM excursion, peak CoM excursion and peak time. There was a significant main effect for group for AUC ML CoM excursion ($p = 0.017$) with the CP group showing a higher CoM excursion than the TD group (Figure 2.3A), indicating an overall magnified response in the CP group to visual perturbations. The CP group reached higher average peak CoM excursion than TD on both sides (Figure 2.3B), but this group effect was not statistically significant ($p = 0.093$), nor was the side or group by side interaction. There was a significant group effect for the peak timing of CoM excursion ($p = 0.031$), with the CP group averaging higher peak times compared to the TD group, i.e., they reached peak CoM excursion later than TD (Figure 3C). There was also a significant main effect for side for peak timing ($p = 0.042$), where both CP and TD groups reached the peak CoM excursion quicker on their more affected side compared to their less affected side. Full details of the statistical analysis are provided in Table 2.4 in the supplementary material.

Table 2.3: Mean and 95% confidence interval for CP and TD groups on the more affected and less affected side

	Group	More Affected side			Less Affected side		
		Mean	95%CI		Mean	95%CI	
AUC ML CoM excursion (m·s)	CP	0.170	0.136	0.203	0.171	0.131	0.211
	TD	0.116	0.052	0.181	0.076	0.024	0.128
Peak ML CoM excursion (m)	CP	0.087	0.071	0.103	0.089	0.071	0.107
	TD	0.075	0.046	0.104	0.058	0.039	0.076
Peak Time (s)	CP	2.484	2.229	2.738	2.615	2.309	2.922
	TD	2.005	1.829	2.182	2.310	1.883	2.737
Step Placement-1st step (m)	CP	-0.002	-0.004	0.000	-0.003	-0.005	-0.001
	TD	-0.006	-0.009	-0.004	-0.004	-0.007	0.000
Step Placement-averaged over 3steps (m)	CP	-0.008	-0.011	-0.005	-0.007	-0.010	-0.004
	TD	-0.002	-0.005	0.001	-0.002	-0.005	0.002
Subtalar angle (degrees)	CP	-0.031	-0.100	0.038	0.065	0.002	0.128
	TD	0.178	0.032	0.325	0.057	-0.080	0.195
Peroneal EMG (%)	CP	-0.017	-0.044	0.009	-0.002	-0.016	0.013
	TD	-0.012	-0.024	-0.001	-0.011	-0.042	0.019

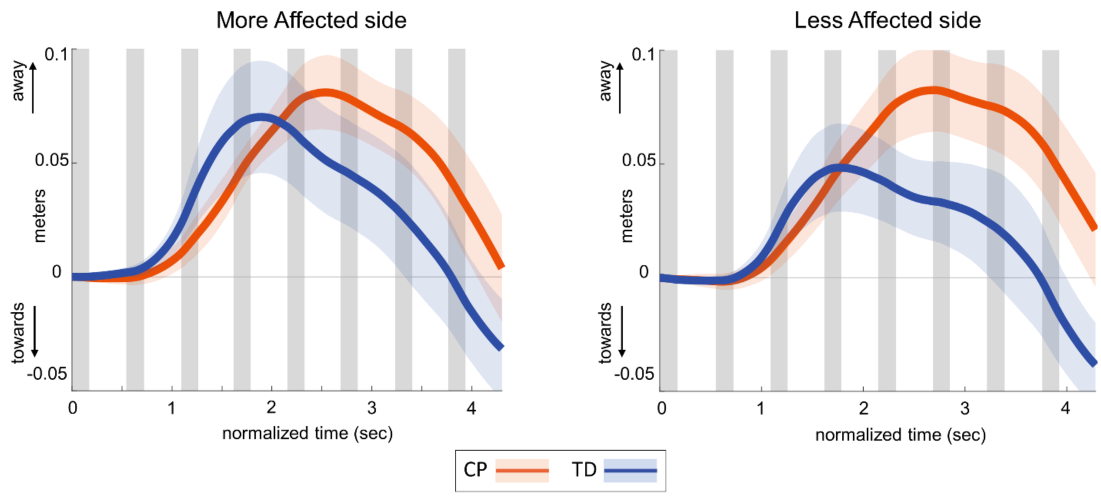

Figure 2.2: Group average trajectories for medio-lateral center of mass excursion in response to visual fall stimuli in CP (orange) and TD (blue). Thick gray line along zero at X-axis indicates the mean of control (no fall stimulus) steps, which is subtracted from stimulus data. Shaded areas around each trajectory represent 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with double-stance (gray shading) and single-stance (no shading).

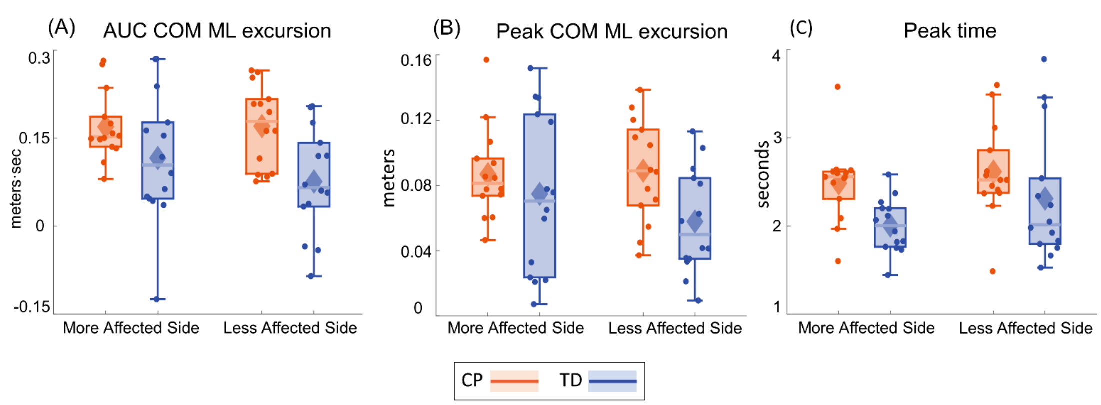

Figure 2.3: Box and whisker plots, with scattered dots indicating each subject, for AUC ΔCOM M-L excursion (Panel A), Peak ΔCOM M-L excursion (Panel B) and Peak time of ΔCOM M-L excursion (Panel C) for CP (orange) and TD (blue) groups on the more affected (left) and less affected (right) side.

2.5.2 Ankle Roll Response

Figure 2.4 shows the group average trajectories subtalar angle and Figure 2.5 shows the box and whisker plots for the AUC for subtalar angle for the stance foot during the first single stance following the visual perturbation. The integrated subtalar angle showed a significant group by side interaction ($p = 0.047$). Post-hoc comparisons revealed that both CP and TD groups exhibited a similar increase in subtalar inversion on the less affected side ($p = 0.221$). On the more affected side, however, the TD group showed a significantly higher inversion at the subtalar joint compared to the CP group ($p = 0.003$). This response in the ankle roll mechanism is supported by the peroneal EMG data, which showed a localized reduction in peroneal activity during the first post-perturbation single stance in the more affected side of the TD group. Reduced peroneal EMG activity is indicative of reduced eversion and in turn suggestive of increased inversion. Figure 2.6 shows the group average trajectories for peroneal EMG and Figure 2.7 shows the box and whisker plots for the AUC of peroneal EMG for both groups. There was a greater reduction in peroneal muscle activity in TD compared to the CP group, however, this between group difference was not significant ($p = 0.458$).

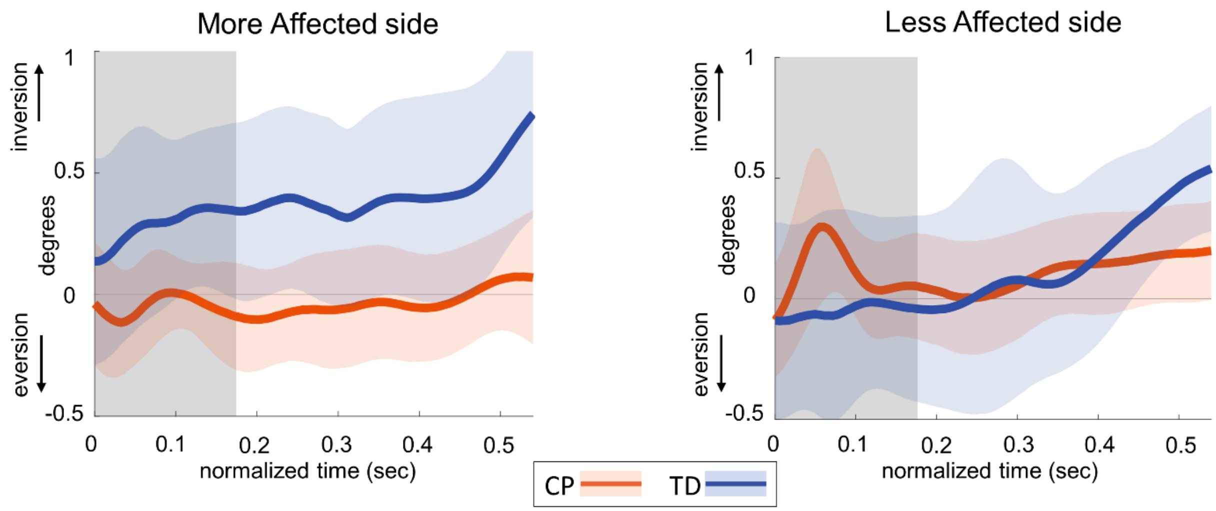

Figure 2.4: Group average trajectories for subtalar angle during the first post-stimulus step following a visual fall perturbation in CP (orange) and TD (blue). Thick gray line along zero at X-axis indicates the mean of control (no fall stimulus) steps, which is subtracted from stimulus data. Shaded areas around each trajectory represent 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with double-stance (gray shading) and single-stance (no-shading). Positive and negative Y-axis indicates inversion and eversion respectively.

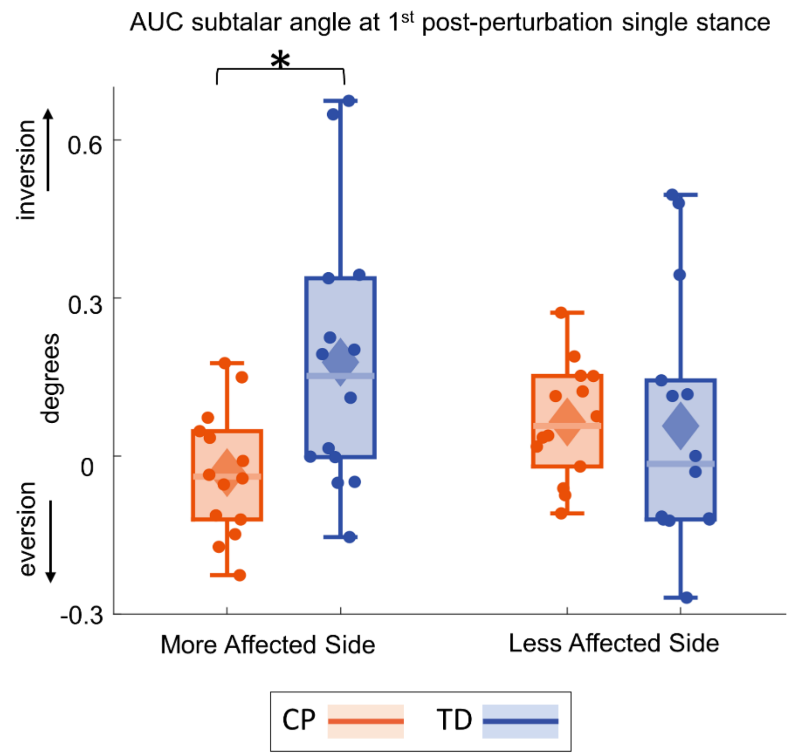

Figure 2.5: Box and whisker plots, with scattered dots indicating each subject, for AUC Δsubtalar angle for CP (orange) and TD (blue) groups on the more affected (left) and less affected (right) side. Asterisk indicates $p<0.05$ for post-hoc pairwise comparisons.

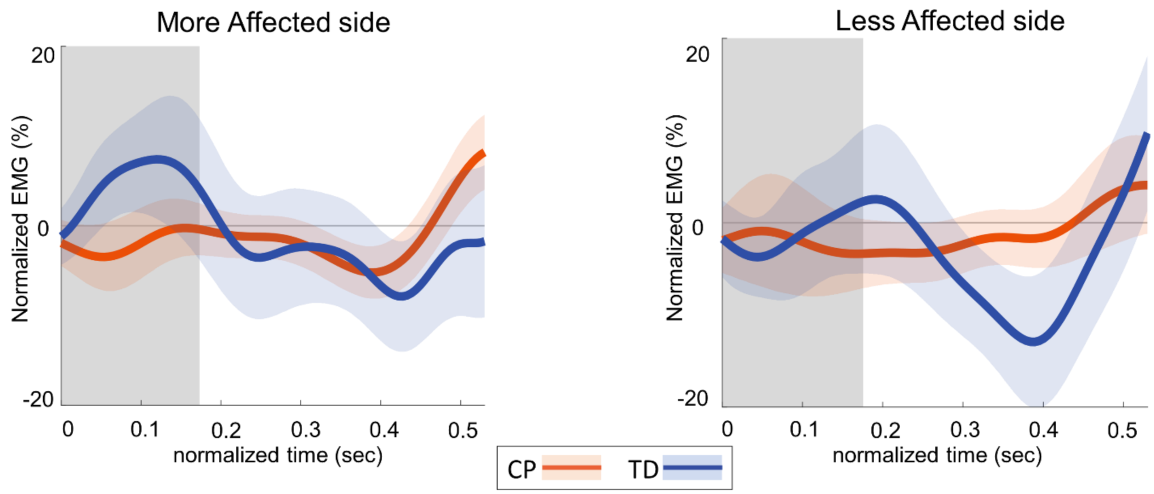

Figure 2.6: Group average trajectories for peroneal EMG during the first post-stimulus step following a visual fall perturbation in CP (orange) and TD (blue). Thick gray line along zero at X-axis indicates the mean of control (no fall stimulus) steps, which is subtracted from stimulus data. Shaded areas around each trajectory represent 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with double-stance (gray shading) and single-stance (no shading). Y-axis indicates EMG data normalized to average EMG of no perturbation steps.

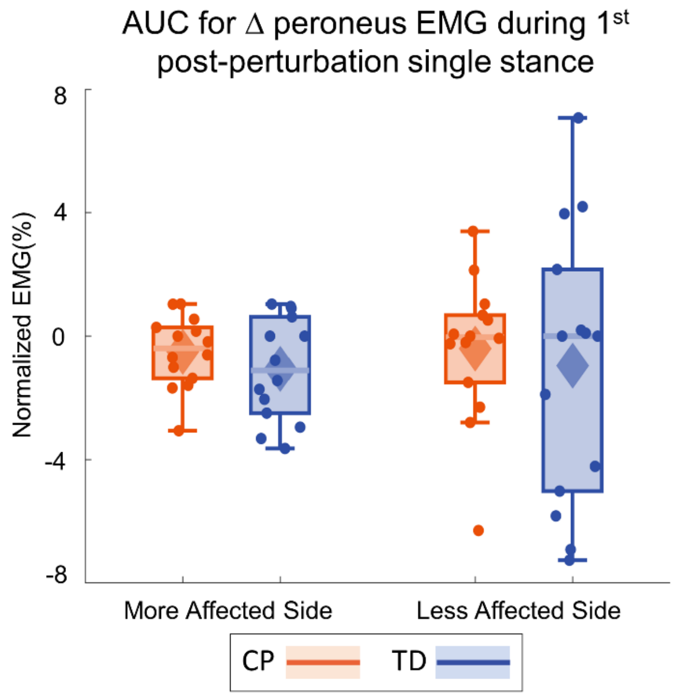

Figure 2.7: Box and whisker plots, with scattered dots indicating each subject, for AUC Δperoneus EMG for CP (orange) and TD (blue) groups on the more affected (left) and less affected (right) side.

2.5.3 Foot Placement Response

Figure 2.8 shows the foot placement changes for the first four steps following the visual perturbation. Figure 2.9 shows the box and whisker plots for the average foot placement response across the first three post-perturbation steps. At the first post-perturbation step, the TD group showed a greater foot placement response towards the direction of the fall stimulus compared to the CP group on both sides. This difference between the CP and TD groups was small (~4 and 1 mm respectively on the more affected and less affected side, Figure 2.8) and was not statistically significant ($p = 0.058$). The average foot placement response over the first three post-perturbation steps, however, showed a significant group effect (p = 0.007). The CP group showed a higher foot placement response compared to the TD group over the first three post-perturbations steps, indicating a higher overall foot placement response in the CP group.

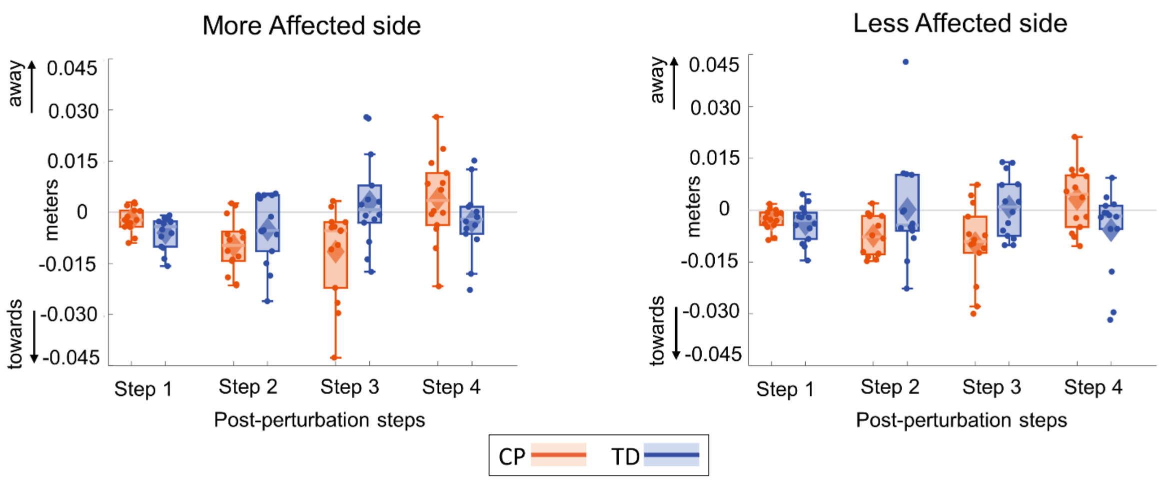

Figure 2.8: Box and whisker plots for foot placement response for the first four steps following a visual fall perturbation in CP (orange) and TD (blue). Thick gray line along zero at X axis indicates the mean of control (no fall stimulus) steps, which is subtracted from perturbation data.

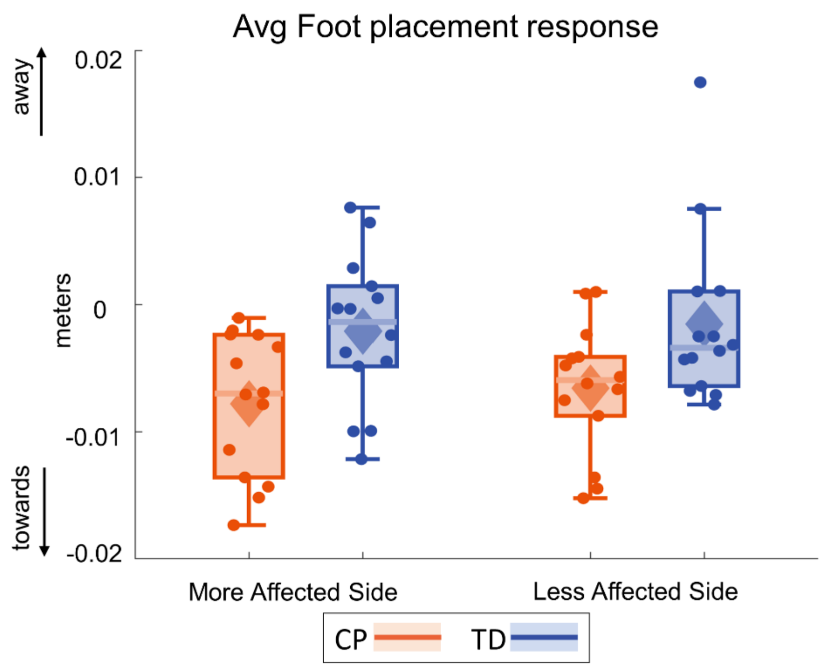

Figure 2.9: Box and whisker plots, with scattered dots indicating each subject, for average foot placement response over first three post-perturbation steps for CP (orange) and TD (blue) groups on the more affected (left) and less affected (right) side.

2.6 Discussion

Our study investigated the role of visual input in walking balance control in individuals with CP and age- and sex-matched peers. We used virtual reality to induce visual fall stimuli and observed the resulting lateral shift in the whole-body CoM and the immediate responses in the foot placement and ankle roll balance mechanisms that generate the whole-body response. Our study provides compelling evidence that individuals with CP rely more on visual information compared to typically developing peers. As hypothesized, visual perturbations induced significantly larger CoM responses in the CP group compared to the TD group. Furthermore, the CP group used the foot placement balance mechanism more and the ankle roll balance mechanism less.

Participants moved their body away from the direction of the visual fall, as would be an appropriate response if they were actually falling during walking in a real-life environment. For example, if you bump into someone and are pushed to the right by the impact, then you would want to move your body to the left to arrest the fall. With the exception of the three participants from CP group that were excluded from the analysis, both CP and TD groups demonstrated this CoM shift in the away direction. In the CP group, this CoM response was larger and peaked later than in the TD group. This increased CoM shift is similar to the magnified sway response seen in standing balance studies in individuals with CP [12,51], and in older adults [66]. Older adults showed a similarly magnified and variable CoM excursion response to continuous visual perturbations during walking [18]. The magnified CoM response in the above studies has been attributed to problems in sensory re-weighting, related to age or pathology. Our results extend these hypotheses to walking balance control in individuals with CP. The magnified CoM response during walking implies that individuals with CP are more affected by changes in the visual environment and suggest increased reliance on vision over sensory modes for walking balance control. In addition to differences in the overall CoM movement, we also investigated differences in the balance mechanisms used to generate the whole-body movement by modulating force against the ground. As hypothesized, individuals with CP demonstrated reduced ankle response and magnified foot placement response. The TD group showed ankle roll and foot placement responses that were similar to that of typical healthy adults [54]. They showed an ankle roll response in the first step after the onset of the visual perturbation. In contrast, in individuals with CP the ankle roll response was reduced compared to TD. With respect to immediate foot placement response, the foot placement response in the CP group was also lesser than that of the TD group. However, the CP group did show a large foot placement response in the second and third post-stimulus steps. Thus, their overall average response over the first three steps was more magnified compared to the TD group. In summary, the TD group were able to return their response to their "normal" no perturbation gait after the first post-perturbation step. In contrast, the CP group had an overall increased foot placement response across the first three steps before they could return to their normal no-perturbation gait.

While we expected the participants with CP to perform worse on the affected side compared to the TD peers, we only found a group by side interaction for subtalar angle i.e., the CP group did significantly worse compared to the TD on affected side. We found a group effect for most of our variables, including the primary outcome measure of AUC COM excursion and Peak time as well as the secondary outcome measures of foot placement i.e., irrespective of their side, the CP group overall did significantly worse compared to the TD group. A potential reason is that we had only had four individuals with hemiplegia in our study while the remaining participants had diplegia. A higher number of individuals with hemiplegia would have led to starker differences between the two sides.

Individuals with CP had reduced responses in the ankle roll mechanism and increased responses in the foot placement mechanism. Studies in standing balance have shown that individuals with TD use a distal to proximal organization of balance responses to mechanical perturbations, with the ankle being recruited first and the hip last. Individuals with CP tend to use a different pattern that favors the proximal joints, producing multiple bursts of torque at hip, knee, and ankle joint simultaneously, indicating that they are unable to make quick, precise, and finer adjustments through distal control at the ankle [48]. Our results provide evidence of similar preference of proximal over distal strategies during walking balance control in CP.

Another potential reason for the reduced ankle roll is the higher cadence and reduced step time in the CP group compared to the TD group. In neurotypical adults, the dominant balance response shifts between the ankle roll and foot placement mechanism depending on the walking cadence[67]. Lower cadences lead to longer single stance duration, with longer time to apply force using the ankle roll mechanism, which reduces the need for a foot placement response. Conversely, walking at higher cadences results in lower single stance duration, leading to reduced opportunity for the ankle roll mechanism. At the same time, frequent foot placements at higher cadences provide more opportunity for foot placement control. Our cohort of individuals with CP walked with similar velocity, but at a higher average cadence. It is possible that the differences in balance mechanisms between groups are a consequence of this difference in cadence, i.e., that people with CP use less ankle roll because they walk at higher cadence.

It is also possible that the magnified CoM response in CP is due to motor deficits. Motor impairments at the ankle, such as inability to generate appropriate and timely muscle contraction due to spasticity, could lead to the observed lack of ankle roll use in the CP group. While we excluded individuals with severe spasticity (Modified Ashworth Scale > 4), mild spasticity might still impair the relatively precise modulations required for the ankle roll mechanism. Our hypothesis that impaired somatosensory and proprioceptive processing causes balance problems in CP predicts the increased CoM response and altered balance mechanisms we observed here, but other explanations, such as motor deficits or increased cadence in CP precluding use of the ankle roll mechanism cannot be excluded by our results. Interestingly, if it is true that individuals with CP do not have access to the ankle roll due to motor impairments, this might *cause them* to walk with higher cadence, because stability at lower cadence depends on the ankle roll mechanism, which they do not have access to. More research is needed to distinguish between these possible explanations of the observations in this study.

Lastly, visual impairments in individuals with CP can broadly be due to ocular disorders or due to a non-ocular, brain-based processing disorder i.e., cerebral visual impairment (CVI) ([68–70]. While we excluded any individuals with any ocular impairments as well as known diagnosis of CVI, given how complex and challenging the diagnosis of CVI is, it is possible that some individuals in the study had impaired processing of visual information. Previous research has shown that children with CP were slower to detect a directional change in visual motion and made more errors in identifying the change compared to the control group[71]. These higher reaction times in individuals with CP could be a potential reason behind the CP group in our study having higher peak times compared to their TD peers. However, despite potential visual impairments, these individuals had more magnified responses to visual perturbations, as evidenced by higher AUC COM excursion, and thus, relied more on vision for balance control. This may indicate that despite impaired processing of both visual and proprioceptive information, individuals with CP prioritized visual input over proprioceptive input for walking balance. While proprioceptive deficits at the lower extremity have been related to standing balance[11], it is likely that a similar relationship may exist between visual reliance and proprioceptive deficits. Thus, those individuals with greater proprioceptive deficits may show a greater reliance on vision. In such individuals, assistive walking devices would not only serve its primary biomechanical function of improving base of support, reduction of lower limb loads and providing propulsion and braking but it may help in augmentation of somatosensory cues by providing additional information about the spatial orientation of the body[72].

2.6.1 Limitations

Our study only included individuals with CP who were able to independently ambulate without any walking aids for multiple bouts of 2 minutes (GMFCS levels I and II), mainly to reduce the possibly confounding influence of tactile or visual feedback from handrails during visually perturbed walking. Individuals with lower functional mobility may respond differently to visual perturbations while walking. Second, there may be some baseline differences in the walking characteristics of individuals with CP and TD that are secondary to the neuromotor deficits due to CP. E.g., individuals with CP walked with a higher cadence and shorter step time compared to those with TD. It is possible that such differences, in addition to neuromotor deficits, contribute indirectly to the group differences in responses to visual perturbations observed here. Probing whether the group differences are due to neuromotor deficits only or due to the differences in gait characteristics of CP and TD group, however, is beyond the scope of this study and should be subject of future research.

2.7 Conclusion

Individuals with CP demonstrated a magnified and delayed response to visual perturbations. They were more affected by changes in visual cues and relied more on visual information for walking balance control. Our findings suggest that individuals with CP may alter the relative contribution of visual input in active control of walking balance, commonly referred to as sensory reweighting[42]. Also, individuals with CP showed increased use of the foot placement mechanism for balance control and diminished use of the ankle roll mechanism. This suggests a reliance on proximal over distal control of walking balance in individuals with CP, similar to what other studies observed in standing. These findings provide insight into how sensory information is processed for balance control during walking by individuals with CP and which motor responses they prefer to adopt in response to perceived threats to their balance. This information will be critical in planning treatment targeted towards addressing specific deficits in walking balance and fall prevention in CP. The current standard of care for CP largely focusses on motor-related deficits such as muscle weakness, spasticity, contractures, and reduced flexibility with mixed outcomes [19–22]. Our findings highlight the need for sensory-based therapeutic approaches that address somatosensation and proprioception in addition to the current motor-centric treatments to provide a more comprehensive approach to balance rehabilitation in individuals with CP.

2.8 Data Availability

The datasets generated and analyzed in this study can be found at the below link. Sansare, Ashwini; Reimann, Hendrik (2022), Neuromotor Control of Walking Balance in Individuals with Cerebral Palsy, Dryad, Dataset.
https://doi.org/10.5061/dryad.1ns1rn8x2

2.9 Ethics Statement

The studies involving human participants were reviewed and approved by the University of Delaware Institutional Review Board. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

2.10 Author contributions

AS, HR, and SL: conception and design of the work. AS, MA, and HR: data collection and critical revision. AS and HR: analysis of data and interpretation. AS: drafting the work. AS, MA, SL, JJ, and HR: revision and final approval of the work. All authors agreed to be accountable for the content of the work.

2.11 Funding

AS was funded by the Unidel Distinguished Scholars Award and in part by a Promotion of Doctoral Studies (PODS) II Scholarship from the Foundation for Physical Therapy Research. HR was supported by the Parkinson's Foundation (PFJFA-2036).

2.12 Acknowledgements

We would like to thank all the participants and their parents who contributed to the study.

2.13 Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2.14 Supplementary Material

Table 2.4: Statistical analysis for within-subject (side and group*side) and between-subject (group) effects

Outcome Measure	Effect	df	F statistic	p value	Partial eta squared
AUC M-L COM excursion (meters*sec)	group	[1,26]	6.451	**0.017**	0.199
	side	[1,26]	2.055	0.164	0.073
	group*side	[1,26]	2.284	0.143	0.081
Peak M-L COM excursion (meters)	group	[1,26]	3.037	0.093	0.105
	side	[1,26]	1.582	0.220	0.057
	group*side	[1,26]	2.636	0.117	0.092
Peak Time (seconds)	group	[1,26]	5.193	**0.031**	0.166
	side	[1,26]	4.585	**0.042**	0.150
	group*side	[1,26]	0.725	0.402	0.027
Foot Placement-1st step (meters)	group	[1,26]	3.921	0.058	0.131
	side	[1,26]	1.342	0.257	0.049
	group*side	[1,26]	3.729	0.064	0.125
Foot Placement-averaged over 3steps (meters)	group	[1,26]	8.604	**0.007**	0.249
	side	[1,26]	0.385	0.540	0.015
	group*side	[1,26]	0.080	0.780	0.003
Subtalar angle (degrees)	group	[1,26]	4.017	0.056	0.134
	side	[1,26]	0.056	0.814	0.002
	group*side	[1,26]	4.336	**0.047**	0.143
Peroneal EMG (%)	group	[1,23]	0.571	0.458	0.024
	side	[1,23]	0.030	0.865	0.001
	group*side	[1,23]	0.000	1.000	0.000

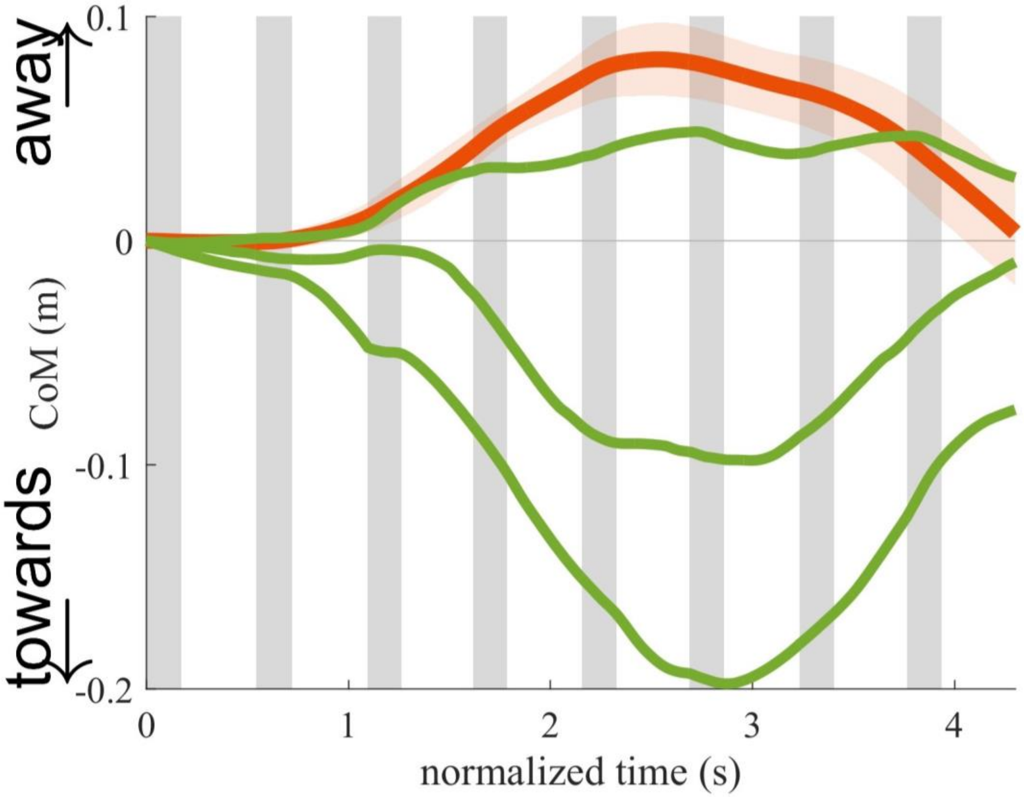

Figure 2.10: Average center of mass (CoM) trajectories for each of the three excluded participants from the CP group (green) and the group average trajectory for all participants in the CP group (orange) with the shaded area showing 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with the double-stance (gray shading) and single-stance (no-shading).

Chapter 3

SUBTHRESHOLD ELETRICAL NOISE ALTERS WALKING BALANCE CONTROL IN INDIVIDUALS WITH CEREBRAL PALSY

3.1 Preface

The following chapter reflects Aim 2 of this dissertation and was submitted to the journal Gait & Posture on January 19th, 2023. A revision was submitted on March 26th, 2023, and is currently under review. This chapter incorporates the reviewer feedback and reflects the most updated version of the manuscript under review. If this work is published prior to the final submission of this dissertation to the University of Delaware, I will request permission from the journal to reproduce this work in my dissertation document. The work was authored (in order) by:

Sansare A, Reimann H, Crenshaw J, Arcodia M, Verma K, Lee SCK.

3.2 Abstract

Sensory deficits in individuals with cerebral palsy (CP) play a critical role in balance control. However, there is a lack of effective interventions that address sensory facilitation to improve walking balance. Stochastic Resonance (SR) stimulation involves delivering sub threshold noise to improve balance in patients with sensory deficits by enhancing the detection of sensory input.

Research question: To investigate the immediate effects of SR on walking balance in individuals with and without CP.

Thirty-four participants (17 CP, 17 age-and sex-matched typically developing controls or TD) between 8-24 years of age were recruited. SR stimulation was applied to the muscles and ligaments of ankle and hip joint. An optimal SR intensity during walking was determined for each subject. Participants walked on a self-paced treadmill for three trials of two minutes each using a random order of SR stimulation (SR) and no stimulation (noSR) control conditions. Our primary outcome measure was minimum lateral margin of stability (MOS). Secondary outcome measures include anterior MOS before heelstrike and spatiotemporal gait parameters. We performed two-way mixed ANOVAs with group (CP, TD) as between-subject and condition (noSR, SR) as within-subject factors.

Compared to walking without SR, there was a small but significant increase in the lateral and anterior MOS with SR stimulation, implying that a larger impulse was needed to become unstable, in turn implying higher stability. Step width and step length decreased with SR for the CP group with SR stimulation. There were no significant effects for other spatiotemporal variables.

Sub threshold electrical noise can slightly improve walking balance control in individuals with CP. SR stimulation, through enhanced proprioception, may have improved the CP group’s awareness of body motion during walking, thus leading them to adopt a more conservative stability strategy to prevent a potential fall.

3.3 Introduction

Cerebral Palsy (CP) is a non-progressive disorder of movement and posture due to an injury to the developing fetal or infant brain. It is characterized by motor deficits such spasticity, muscle weakness and altered motor control as well as sensory deficits such as impaired joint position sense, vibration, two-point discrimination and light touch [11,16,73–75].

Several studies have investigated how sensory deficits are linked with poor motor function and balance control. Kurz et al. showed the magnitude of error in motor performance [6] and mobility impairments in CP, including slower walking speed and shorter steps[9], are associated with abnormal somatosensory cortical activity. Additionally, hip joint proprioception deficits are correlated with poor postural sway in standing and reduced gait speed [10]. Impairments in the ability to perceive vibrations at the ankle and foot, two-point discrimination, and joint position sense are correlated with poor standing balance and impaired motor function[11]. These studies show a strong relationship between sensory deficits and balance function in CP.

Despite compelling evidence supporting the role of sensory processing as a key component in balance control, there is a lack of effective interventions that include sensory facilitation. While a variety of therapeutic interventions have addressed musculoskeletal deficits such as muscle weakness, spasticity, poor flexibility, and contractures, with mixed or unsuccessful outcomes [19–22], there is limited consideration of improving sensory function. The possibility of reversing somatosensory deficits with targeted sensory therapy has been demonstrated through a randomized control trial on adults with CP, which showed improvement in pain thresholds after somatosensory therapy[23], and a neuroimaging study, which demonstrated the plasticity of white matter tracts after physical therapy and botox injections [24]. Therefore, there is a potential to improve sensory regulation of balance control with sensory-centric modalities that can augment proprioceptive feedback while walking.

We address the need for improved sensory regulation in this study through the application of stochastic resonance stimulation (SR). SR stimulation induces a random, sub-sensory noise that does not cross the detection threshold itself but can help a weak sensory signal to cross membrane threshold to be detected [26–28]. Application of SR has significantly improved standing balance in patients with functional ankle instability (FAI)[29,76], diabetic neuropathy, stroke, and in older adults[31,77]. In walking, older adults and frequent fallers have shown reduced variability in their spatio-temporal gait parameters [29,33] with SR stimulation, which indicates improved regularity and rhythmicity of gait. SR stimulation significantly improved postural sway of children with CP compared to a no stimulation condition in standing [43]. Moreover, these improvements in standing balance using SR were significantly larger in the CP group compared to their age-matched typically developing peers. It is yet to be determined, however, if these results can transfer over to walking. Walking is inherently a more complex and unstable activity than standing because the body configuration changes substantially across the gait cycle. More importantly, about 55% of the falls in individuals with CP occur in walking, an additional 39% of falls occur during walking related activities such as turning, bending, and lifting [4].

The aim of this study was to investigate the immediate effects of SR stimulation on balance control of walking in individuals with and without CP. We assessed walking balance using the minimum lateral Margin of Stability (MoS) as the primary outcome measure. Previous work has shown that the lateral stability is altered in children with CP compared to their peers [78]. We hypothesized that SR stimulation would lead to increased minimum lateral MoS compared to no SR stimulation, with higher increases in the CP group than those with typical development. We also assessed anterior MoS immediately before heelstrike and spatiotemporal gait parameters as secondary outcome measures.

3.4 Methods

3.4.1 Participants

Seventeen ambulatory individuals and adolescents with spastic diplegic or hemiplegic CP with Gross Motor Function Classification System (GMFCS) levels I-II [60] and seventeen typically developing (TD) individuals, who were age- (± 6 months) and sex-matched, were recruited through the CP clinic at local hospitals and through flyers, local advertisements, and social media. The sample size was determined through an a priori power analysis that showed at significance $\alpha=0.05$ and power of 0.8, thirty-four participants split equally across two groups (17 CP, 17 TD) are adequately powered to detect a medium effect size ($f=0.25$). The study protocol was approved by the University of Delaware Institutional Review Board and is registered at clinicaltrials.gov (NCT05233748). Appropriate parental consent and child assent were also obtained. Supplementary Table 3.3 shows the inclusion and exclusion criteria.

3.4.2 Instrumentation

Participants walked on a split-belt treadmill (Bertec Inc., Columbus, Ohio, USA) within a virtual reality environment, consisting of a 4-meter-wide corridor of floating cubes (Unity3d, Unity Technologies, San Francisco, CA, USA). The virtual environment was used as a part of a separate visual perturbation protocol that followed the walking trials analyzed in this study. However, for this study specifically, we did not use any visual perturbations and the virtual reality only produced the optic flow of walking along an infinitely long corridor. The treadmill was self-paced, where the treadmill speed adapted in real time to the participant's self-selected speed by keeping the midpoint between the posterior superior iliac spine markers in the anterior-posterior center of the treadmill, using a custom Labview program (National Instruments Inc., Austin, TX, USA). A safety harness was used at all times to protect against falls. Figure 3.1 shows the experimental setup. A 13-camera motion capture system (Qualysis Inc., Gothenberg, Sweden) and a full body Plug-in Gait marker set[62] was used to measure full body kinematics. We recorded marker data at 200 Hz and ground reaction forces and moments at 1000 Hz. We processed force plate data using a low pass filter with a 4th order Butterworth filter at a cut-off frequency of 20 Hz. We determined heel strike and push off events as the maxima and minima of the heel marker relative to the midpoint of the pelvis markers in anterior-posterior direction.

3.4.3 Stochastic Resonance Stimulation

The system consists of six stimulators (STMISOLA, Biopac Systems, Inc., Goleta, USA). The SR signal (Uniform White Noise) was generated by a custom LabView program. SR intensity is defined as the interval of the uniform noise. Self-adhesive electrodes were placed over the ankle (anterior talofibular and deltoid ankle ligaments), and shank (lateral soleus, peroneus longus, and tibialis anterior muscles) and at the hip (posterolateral and inferior to greater trochanter, respectively, to stimulate the gluteus maximus, gluteus medius and the hip joint capsule).

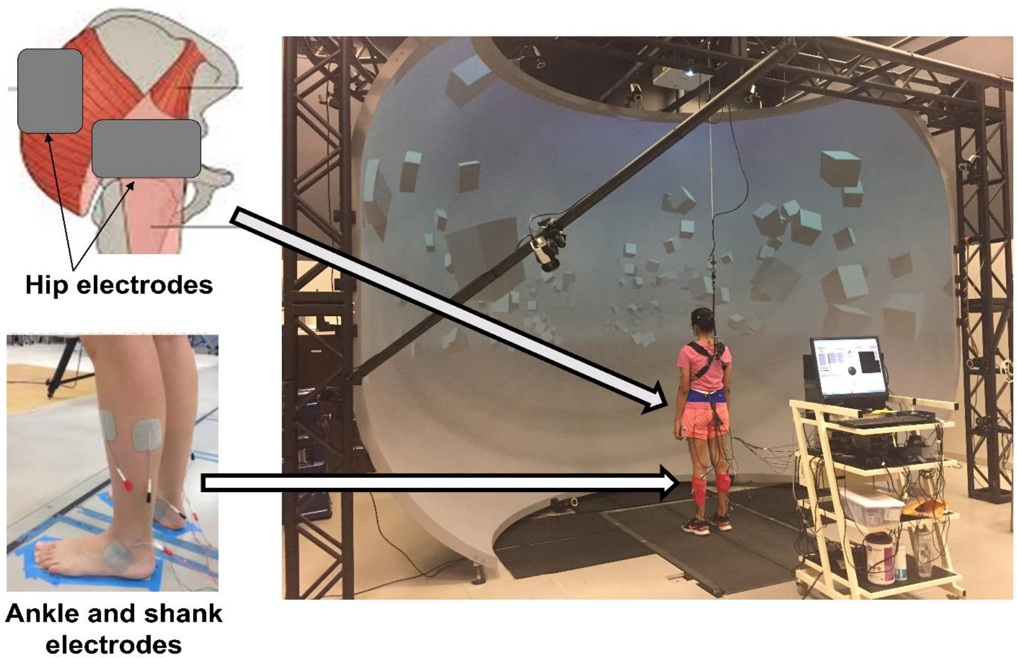

Figure 3.1: Experimental setup. The cart contained the computer that generated the SR signal and six stimulators that delivered SR stimulation via surface electrodes at the hip, shank, and ankle. The electrode leads were long enough to allow unencumbered walking at self-selected pace on the treadmill and were secured around the shank using a 3M Coban self-adhesive wrap. Figure for ankle electrode adapted from Zarkou et al[43].

3.4.4 Protocol

Participants were given at least one 2-minute practice trial to get accustomed to the self-pacing feature of the treadmill and the virtual environment. If the participants were not comfortable with the treadmill and virtual environment, additional practice trials were offered.

The experimental protocol is outlined in Figure 3.2 and is as follows:

SR Sensory Threshold: We determined each participant's individual sensory threshold, defined as the minimum level of stimulation required for an individual to detect a tingling sensation at the stimulation site. Participants walked on a treadmill at a comfortable pace and the stimulation intensity was increased in increments of 0.1 mA, starting at zero, until the participant reported feeling the stimulation. To verify this threshold, the intensity was decreased until the participant could no longer feel the stimulation. This procedure was repeated three times for each stimulation site, and the sensory threshold for that site was defined as the lowest value over the three repetitions.

Determine Optimal SR Intensity: Because the SR effect is sensitive to the stimulus intensity, we determined an optimal intensity for each individual participant. Participants completed three two-minute walking trials in each of four conditions: SR stimulation at 25%, 50%, 75%, and 90% of their individual sensory threshold, in randomized order. As a balance measure, we calculated the average minimal lateral margin of stability for each trial (see Data Analysis below for details). The intensity with the largest minimal MoS was defined as the optimal intensity.

Assess the effect of SR walking balance: Participants completed three two-minute walking trials in each of two conditions: SR stimulation at optimal intensity (SRopt) and no stimulation (no SR) as a control condition, in randomized order.

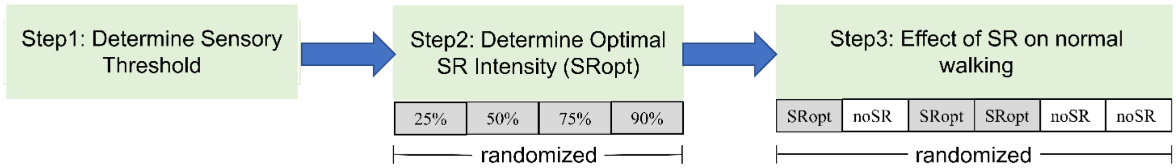

Figure 3.2: Experimental protocol

3.4.5 Data Processing

We computed inverse kinematics for a 15-segment biomechanical model using OpenSim 4.0 [62] and performed further data processing using custom scripts in MATLAB (The MathWorks, Inc., Natick, Massachusetts, United States).

We had a mixed cohort of individuals with diplegia and hemiplegia, and because the less affected side can behave differently in a subject with hemiplegia compared to that of diplegia, we decided to analyze data from the more affected and less affected side separately. The more affected side was defined as the one with hemiplegia in individuals with hemiplegic CP, the one self-identified as the more affected side in individuals with diplegic CP, and the non-dominant side for individuals with TD. The dominant side in the TD group was self-determined by the participants as their preferred lower limb of use during daily activities.

The MOS was calculated as the difference between the extrapolated center of mass (XCOM) and the base of support (BOS), where XCOM is defined as:

$$XCOM = \left(COM + \frac{vCOM}{\sqrt{\frac{g}{l}}} \right)$$

COM = Center of Mass position, *vCOM* = Center of Mass velocity, *g* = gravitational acceleration (9.81m s^{-2}), *l* = instantaneous pendulum length = distance between COM and stance limb ankle joint center, and BOS or base of support limit = 5th metatarsal marker position. The primary outcome measure, minimum lateral MOS, was computed as the minimum of the MOS in the medial-lateral direction for each step, with step defined as heelstrike to heelstrike. A secondary outcome was the anterior MOS before heelstrike, representing the maximum instability in the sagittal plane, computed as the MOS in the anterior-posterior direction just before the heelstrike (at 99% of the gait cycle). A larger MOS implies a larger impulse is needed to become unstable, and in turn implies higher stability. We examined the change in the MOS with SR application (MOS during walking with SR - MOS during walking without SR), such that a positive value implies an increase in MOS, and in turn, an increase in the impulse needed to cause instability, and is more protective against a lateral or an anterior fall. Further, we also assessed the change in the variability of MOS by assessing the effect of SR application on the standard deviation of MOS. Additional secondary outcome measures were the spatiotemporal gait parameters (a) step width, (b) step length, (c) step time, (d) cadence, (e) walking speed, (f) percentage single and double support time. All outcome measures were calculated for each step, then averaged across all steps of one trial.

3.4.6 Statistical Analysis

Data were analyzed using separate two-way mixed ANOVAs, with group (CP, TD) as the between subject factor and condition (noSR, SR) as the within-subject factor. We assessed assumptions of homoscedasticity and normality, respectively, by Levene’s and Shapiro-Wilk tests in addition to visual examination. Between group differences for baseline characteristics such as age and body mass index (BMI) were assessed using paired samples t-test.

3.5 Results

All thirty-four participants completed the study without having any adverse effects. The demographic data for both groups is reported in Table 3.1. The descriptive statistics for outcome measures are reported in Table 3.2. Full details of the statistical analysis are provided in Supplementary Table 3.4.

Table 3.1: Demographic data at baseline for CP and TD groups

	CP (n=17)	TD (n=17)	
	Mean ± SD	Mean ± SD	p value
Age (years)	16.3 ± 4.3	16.1 ± 4.2	0.27
BMI (kg/m^2)	19.0 ± 3.1	23.6 ± 4.7	0.011
Cadence (steps/min)	113 ± 12	106 ± 7	0.07
Walking speed (m/sec)	0.955 ± 0.181	1.030 ± 0.156	0.206
Step Width (m)	0.143 ± 0.063	0.095 ± 0.041	0.012
Step Length: More affected side (m)	0.505 ± 0.078	0.582 ± 0.079	0.008
Step Length: Less affected side (m)	0.506 ± 0.073	0.582 ± 0.078	0.006
Step Time: More affected side (sec)	0.534 ± 0.071	0.564 ± 0.040	0.137
Step Time: Less affected side (sec)	0.551 ± 0.067	0.574 ± 0.041	0.243

Table 3.2: Descriptive statistics (mean and 95% confidence interval for noSR and SR conditions for CP and TD groups

More Affected Side													
	Group	CP			TD			CP			TD		
		Mean	95%CI		Mean	95%CI		Mean	95%CI		Mean	95%CI	
Minimum ML MOS	noSR	0.097	0.086	0.108	0.083	0.072	0.094	0.097	0.084	0.110	0.089	0.077	0.102
	SR	0.098	0.087	0.109	0.083	0.072	0.094	0.098	0.085	0.111	0.090	0.077	0.103
Variability (Standard Deviation) of Minimum ML MOS	noSR	0.014	0.011	0.016	0.011	0.008	0.013	0.014	0.012	0.016	0.011	0.009	0.013
	SR	0.014	0.012	0.017	0.011	0.008	0.013	0.014	0.012	0.016	0.011	0.009	0.013
AP MOS before heelstrike	noSR	0.185	0.164	0.206	0.134	0.113	0.155	0.191	0.168	0.215	0.145	0.122	0.169
	SR	0.183	0.162	0.204	0.131	0.110	0.152	0.188	0.163	0.212	0.144	0.119	0.168
Variability (Standard Deviation) of AP MOS before heelstrike	noSR	0.036	0.032	0.040	0.024	0.020	0.029	0.034	0.030	0.038	0.025	0.021	0.029
	SR	0.036	0.033	0.040	0.024	0.021	0.028	0.034	0.031	0.038	0.024	0.021	0.028
Step Length	noSR	0.505	0.466	0.544	0.582	0.543	0.621	0.035	0.029	0.040	0.027	0.022	0.033
	SR	0.500	0.463	0.537	0.577	0.540	0.615	0.035	0.029	0.040	0.028	0.023	0.034
Outcome measures calculated using both sides													
Step Width	noSR	0.144	0.117	0.170	0.095	0.069	0.121						
	SR	0.146	0.120	0.173	0.095	0.068	0.121						

3.5.1 Margin of Stability

3.5.1.1 Lateral MOS

Figure 3.3 shows the average minimum lateral MOS change with SR stimulation in CP and TD groups for both sides. For the more affected side, there was a significant group by condition interaction ($p = 0.028$). Pairwise post hoc comparisons using Bonferroni corrections showed that in the CP group, the average MOS increased with SR compared to noSR condition ($p = 0.018$) by 1 mm whereas in the TD group, the average MOS did not change with SR compared to noSR condition ($p = 0.450$). For the less affected side, there was a significant effect for condition i.e., the SR condition showed an average increase in the MOS compared to the noSR condition in both CP and TD groups ($p = 0.007$). With respect to the effect of SR on variability of minimum lateral MOS, we did not find a significant effect for condition ($p = 0.340$) nor a group by condition interaction ($p = 0.244$).

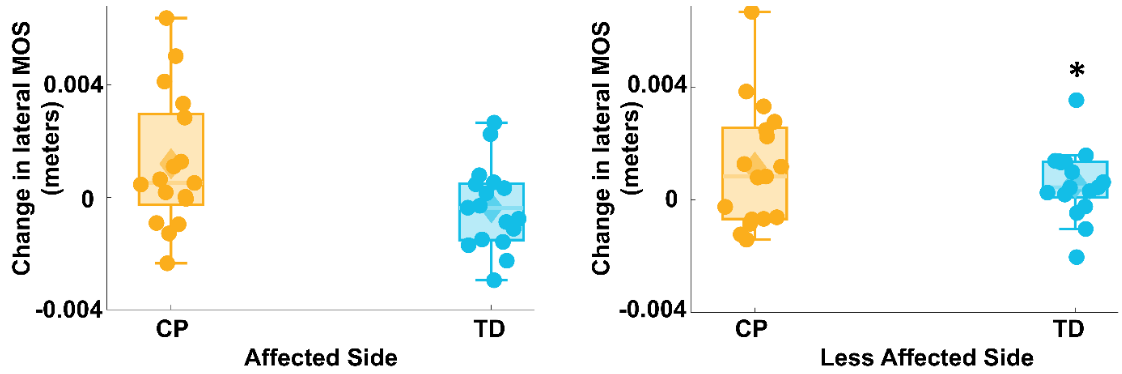

Figure 3.3: Average change in minimum lateral MOS (with SR – baseline without SR) in CP (yellow) and TD (blue) groups for affected (left panel) and less affected (right panel) sides. Asterisks indicate a statistically significant change with SR compared to noSR on post hoc comparisons.

3.5.1.2 Anterior MOS:

Figure 3.4 shows the average change in anterior MOS before heelstrike with SR stimulation in CP and TD groups for both sides. The anterior MOS before heelstrike, for the more affected side, showed a condition effect (p = 0.035) with an average increase of 2 mm in the MOS compared to the noSR condition across groups (medium effect size: partial eta square = 0.131), implying increased stability with SR. A significant group effect occurred; the CP group had an average of 5 cm lesser MOS compared to the TD group. For the less affected side, there was an average increase of 3 mm in MOS with SR compared to noSR condition pooled across both groups, but this difference was not statistically significant (p = 0.058). With respect to the effect of SR on variability of anterior MOS, we did not find a significant effect for condition (p = 0.847) nor a group by condition interaction (p = 0.868).

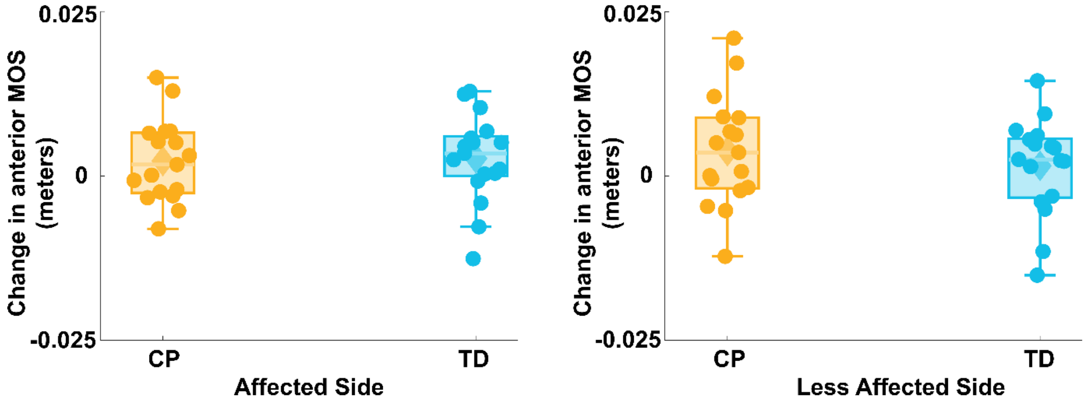

Figure 3.4: Average change in anterior MOS before heelstrike (with SR – baseline without SR) in CP (yellow) and TD (blue) groups for affected (left panel) and less affected (right panel) sides.

3.5.2 Spatiotemporal gait parameters

3.5.2.1 Step Width:

There was a significant group by condition interaction (p = 0.032). Pairwise post hoc comparisons using Bonferroni corrections showed that the CP group increased the average step width with SR compared to the noSR condition (p = 0.012) by 2.7 mm whereas in the TD group, the step width decreased with SR compared to the noSR condition by 1 mm (p = 0.619).

3.5.2.2 Step Length:

There was a significant condition effect, showing that irrespective of the group, step length decreased by 5 mm with SR compared to noSR condition (p = 0.032). Additionally, there was a significant group effect, showing that the step length in the CP group was lower than the TD group by 7.7 cm (p = 0.006).

There were no significant effects for group, condition nor a group by condition interaction for other spatiotemporal variables, including cadence, walking speed, step time, percentage of double support and single support time (Supplementary Table 3.2).

3.6 Discussion

This study compared the immediate effects of applying sub-threshold stochastic resonance stimulation on walking balance in individuals with and without cerebral palsy. We found that there were small but statistically significant changes in the medio-lateral and anterior-posterior stability, step width and step length after SR stimulation in individuals with CP. While the results support our primary hypothesis that enhanced proprioception through SR stimulation will increase the lateral margin of stability, these changes are small. Hence, we believe that SR application alters gait in individuals with CP but the precise effects on medio-lateral stability are complex.

For lateral stability, individuals can increase their MOS by either reducing the excursion of their XCOM or increasing their BOS i.e., their step width [79]. The CP group in our study increased their MOS by increasing their step width with SR stimulation. It may seem counterintuitive for the CP group to increase their lateral MOS when it is already larger than that of their TD peers. A larger MOS, however, implies a higher lateral impulse is needed to cause the XCOM to move out of the BOS, and hence is more protective against a lateral fall. We hypothesize that SR application, by enhancing proprioception, may improve the CP group’s awareness of body motion during walking. Such enhanced awareness may have caused adoption of a protective stability strategy to help prevent a potential lateral fall. However, it is important to note that a change in MOS can be interpreted in more than one way. The participant might feel unstable with the application of additional noise through SR and hence, might increase their MOS to protect against the instability cause due to SR. Thus, an increase in the MOS and step width could be interpreted as a greater need for stability because SR itself caused instability. Hence, while the results of our study show that SR application does cause a change in the lateral stability, the exact implications of SR on fall risk during walking are not yet known.

The anterior MOS increased with SR stimulation in both the groups. Anterior stability just before heel strike would increase by moving the XCOM posteriorly, closer to the BOS. Doing the converse would lead to a XCOM that is further out from the BOS and would need a smaller perturbation to cause a fall in the anterior-posterior plane. Our cohort reduced their step length with SR stimulation, thus bringing their XCOM closer to the BOS, which in turn increased their AP MOS. Reducing step length points towards a conservative protective strategy should an anterior perturbation, such as a trip, were to occur. The fact that both CP and TD groups changed in a similar manner is not surprising because previous work showed no differences in the AP MOS between individuals with CP and TD [80]. Our results are also consistent with another study on typical adults that showed improved lateral stability but no changes in anterior stability with SR during standing [81].

While the above changes in the lateral and anterior MOS, step width and step length are significant and consistent, they are small in magnitude. Moreover, we did not find any significant changes in the variability of MOS nor other spatiotemporal gait parameters such as cadence, walking speed and step time. Our findings are consistent with those of another SR study that showed small improvements across all measures of standing balance in young healthy adults, with significant change on only one outcome measure[82]. There could be two reasons for the modest improvements in our cohort. First, given that with SR, only the CP group changed their lateral stability with no change in the TD group, the magnitude of SR-induced change may be related to their baseline stability and a possible ceiling effect. Because the individuals in our CP group were very high functioning, a more impaired cohort may show greater response to SR stimulation. Second, regular and unperturbed walking may not be challenging enough to induce altered stability with SR. SR is hypothesized to improve balance control by improving sensory regulation. Hence, adding sensory challenges to walking, such as visual perturbations or vestibular stimulation to induce falls, may sufficiently challenge the sensorimotor control of walking balance and be a more appropriate method of assessing the potential difference SR can make. Recent work that applied SR to the trunk and legs in the presence of visual perturbations showed that higher baseline instability following perturbations prior to SR application was associated with greater effects of SR [81]. Acuña et al also showed that improvements with vibrotactile SR in typical adults were significantly related to an individual's baseline performance without SR [82]. Similarly, the effect of vibratory SR in improving balance was greater in elderly fallers with greater balance deficits [83]. Thus, future studies that include individuals with CP who have higher level of impairment (GMFCS level III) may be able to better test the effectiveness of SR. Lastly, prior research has shown evidence of an inverted U-shaped effect for SR, where intensities above and below the "optimal" intensity did not produce as effective results as the optimal intensity. To this end, we included an optimization procedure (Step 2 under the experimental protocol) to determine a participant specific SR intensity prior to beginning the six walking trials that determined the effect of SR on walking balance. While it was not the objective of this study to investigate whether the subjects demonstrated the inverted U-shaped phenomenon, our data showed that participants demonstrated a clear inverted U-shaped effect while some did not (Supplementary figure 3.5). Thus, due to the heterogeneity of participant-specific optimal SR intensities, we cannot verify that the overall group intensity-response curve to be clear inverted U-shape, rather, the observed heterogeneity reinforces the need to determine participant-specific optimal SR intensities.

3.7 Conclusion

SR stimulation led to small improvements in walking balance and an adoption of a more conservative stability strategy in individuals with CP. Our results provide evidence that sub-threshold electrical noise led to altered gait in a high functioning cohort of individuals with CP, the exact implications for stability not yet known.

3.8 Ethics Statement

The studies involving human participants were reviewed and approved by the University of Delaware Institutional Review Board. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

3.9 Author contributions

AS, HR, and SL: conception and design of the work. AS, MA, and HR: data collection and critical revision. AS and HR: analysis of data and interpretation. AS: drafting the work. AS, MA, SL, JJ, and HR: revision and final approval of the work. All authors agreed to be accountable for the content of the work.

3.10 Funding

AS was funded by the Unidel Distinguished Scholars Award and in part by a Promotion of Doctoral Studies (PODS) II Scholarship from the Foundation for Physical Therapy Research and American Society of Biomechanics Grant-In-Aid. HR was supported by the Parkinson's Foundation (PFJFA-2036).

3.11 Acknowledgements

We would like to thank all the participants and their parents who contributed to the study.

3.12 Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3.13 Supplementary Material

Table 3.3: Inclusion and Exclusion Criteria. * denotes criteria applicable to TD group in addition to the CP group

Inclusion	Exclusion
• Age 8 - 24 years • Diagnosis of spastic diplegic or hemiplegic CP • GMFCS classification level I or II (ability to walk independently without assistive device) • Visual, perceptual, and cognitive/ communication skills to follow multiple step commands* • Seizure-free or well controlled seizures* • Ability to communicate pain or discomfort*	• Diagnosis of athetoid, ataxic or quadriplegic CP • History of selective dorsal root rhizotomy • Botox injections in the lower limb (past 6 months) • Severe spasticity of the lower extremity muscles (e.g., a score of 4 on the Modified Ashworth Scale) • Irreversible muscle contractures • Lower extremity surgery or injuries in the past year* • Visual or vestibular deficits*

Table 3.4: Degrees of freedom (df), F statistic, p value and effect sizes (partial eta square)

	Outcome Measure	Effect	df	F statistic	p value	Partial eta squared
Affected Side	Minimum ML MOS	group	[1,32]	3.393	0.075	0.096
		condition	[1,32]	1.478	0.233	0.044
		group*condition	[1,32]	5.280	0.028	0.142
	Variability of Minimum ML MOS	group	[1,32]	3.999	0.054	0.111
		condition	[1,32]	0.940	0.340	0.029
		group*condition	[1,32]	1.408	0.244	0.042
	AP MOS before heelstrike	group	[1,32]	12.560	0.001	0.282
		condition	[1,32]	4.841	0.035	0.131
		group*condition	[1,32]	0.034	0.855	0.001
		group	[1,32]	18.275	<0.001	0.364

	Variability of AP MOS before heelstrike	condition	[1,32]	0.038	0.847	0.001
		group*condition	[1,32]	0.028	0.868	0.001
	Step Length	group	[1,32]	8.554	0.006	0.211
		condition	[1,32]	5.053	0.032	0.136
		group*condition	[1,32]	0.010	0.919	<0.001
	Step Time	group	[1,32]	2.046	0.162	0.060
		condition	[1,32]	0.339	0.565	0.010
		group*condition	[1,32]	0.908	0.348	0.028
	% Single Support Time	group	[1,32]	0.643	0.428	0.020
		condition	[1,32]	0.285	0.597	0.009
		group*condition	[1,32]	0.354	0.556	0.011
Less Affected Side	Minimum ML MOS	group	[1,32]	0.775	0.385	0.024
		condition	[1,32]	8.346	0.007	0.207
		group*condition	[1,32]	0.878	0.356	0.027
	Variability of Minimum ML MOS	group	[1,32]	3.901	0.057	0.109
		condition	[1,32]	0.619	0.437	0.019
		group*condition	[1,32]	0.124	0.727	0.004
	AP MOS before heelstrike	group	[1,32]	7.376	0.011	0.187
		condition	[1,32]	3.861	0.058	0.108
		group*condition	[1,32]	0.673	0.418	0.021
	Variability of AP MOS before heelstrike	group	[1,32]	14.479	<0.001	0.312
		condition	[1,32]	0.103	0.751	0.003
		group*condition	[1,32]	0.014	0.908	0.001
	Step Length	group	[1,32]	4.180	0.049	0.116
		condition	[1,32]	0.191	0.665	0.006
		group*condition	[1,32]	0.252	0.619	0.008
	Step Time	group	[1,32]	1.341	0.255	0.040
		condition	[1,32]	0.060	0.808	0.002
		group*condition	[1,32]	0.012	0.914	<0.001
	% Single Support Time	group	[1,32]	3.411	0.074	0.096
		condition	[1,32]	0.001	0.992	<0.001
		group*condition	[1,32]	0.012	0.914	<0.001
Outcome measures calculated using both sides						
	Step Width	group	[1,32]	7.503	0.010	0.190

	condition	[1,32]	2.353	0.135	0.068
	group*condition	[1,32]	5.035	0.032	0.136
Cadence	group	[1,32]	3.345	0.077	0.095
	condition	[1,32]	0.386	0.539	0.012
	group*condition	[1,32]	0.061	0.807	0.002
Walking speed	group	[1,32]	1.697	0.202	0.050
	condition	[1,32]	2.197	0.148	0.064
	group*condition	[1,32]	0.005	0.944	<0.001
% Double Support Time	group	[1,32]	2.058	0.161	0.060
	condition	[1,32]	0.081	0.788	0.003
	group*condition	[1,32]	0.067	0.797	0.002

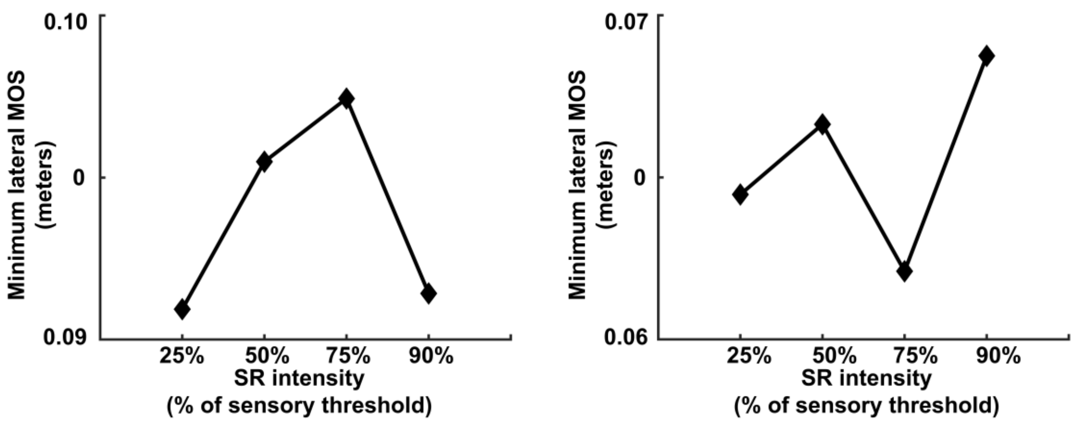

Figure 3.5: Minimum lateral margin of stability (MOS) plotted against the four different SR intensities in two representative participants. Panel A depicts the classic inverted U shape of the SR phenomenon in one participant while panel B shows the curve in another participant that did not demonstrate the inverted U shape phenomenon for SR. In both cases, the intensity that led to greatest increase in minimum lateral margin of stability was selected i.e., 75% for panel A and 90% for panel B.

Chapter 4

IMMEDIATE APPLICATION OF LOW-INTENSITY ELETRCICAL NOISE REDUCED RESPONSES TO VISUAL PERTURBATIONS DURING WALKING IN INDIVIDUALS WITH CEREBRAL PALSY

4.1 Preface

The following chapter reflects Aim 3 of this dissertation and was submitted to the Journal of Neuroengineering and Neurorehabilitation on April 16th, 2023. The preprint is available at: https://www.researchsquare.com/article/rs-2824563/v1

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Sansare A, Arcodia M, Lee SCK, Jeka, J, Reimann H.

4.2 Abstract

Individuals with cerebral palsy (CP) compensate for deficits in somatosensory processing by relying on visual input over proprioception for balance control. Upweighting, i.e., increasing reliance on proprioception, helps free up vision for high-level use like navigation and obstacle avoidance. We hypothesize that children with CP will be able to upweight proprioception and reduce visual reliance if their proprioception is improved. A promising technique to improve proprioception is the use of Stochastic Resonance (SR) stimulation, which uses random, sub-sensory, electrical current to improve proprioception. The aim of this study is to investigate if SR stimulation results in reduced reliance on vision during visually perturbed walking

in individuals with and without CP. We hypothesized that the responses to visual perturbations would be smaller with SR stimulation vs. without SR. We also investigated how the two balance mechanisms driving the responses to the visual perturbations, ankle roll and foot placement, were affected by SR stimulation.

Seventeen ambulatory individuals (age 16.3 ± 4.3, 8 males) with spastic diplegic or hemiplegic CP and seventeen age-and sex-matched individuals with typical development (TD, age 16.1 ± 4.2) were recruited. SR stimulation was applied to the muscles and ligaments of ankle and hip joints. Participants walked on a self-paced treadmill in a virtual reality environment that induced a visual perturbation in the frontal plane once every 10-12 steps. Participants completed three trials of two minutes each of SR stimulation (SR) and no stimulation (noSR) in randomized order. We performed two-way mixed ANOVAs, with group (CP, TD) as between-subject and condition (noSR, SR) as within-subject factors.

The response to visual perturbations was significantly smaller with SR in the CP group ($p<0.001$), but not in the TD group ($p=0.883$). There was no significant effect of stimulation on the use of ankle roll and foot placement in either group.

The reduced response to visual perturbations in the CP group supports our hypothesis that SR stimulation allows children with CP to upweight proprioception and reduce visual reliance. However, the balance mechanisms that are driving these changes in the response to visual perturbation are unclear.

4.3 Introduction

Cerebral palsy (CP) is a neurological disorder that results from an injury to the perinatal brain. In addition to well-known motor deficits such as muscle weakness, spasticity and altered motor control, it also presents with sensory deficits such as, aberrant two-point discrimination, vibration, light touch and joint position sense at ankle and hip[11,16,73,75]. Individuals with CP compensate for sensory deficits, particularly in proprioception, by relying on vision over other senses for balance control [16,17,51]. Such excessive reliance on vision is associated with aberrant balance strategies in individuals with CP [12] and increased fall risk in other clinical populations [13–15].

Visual reliance for balance control has been established in standing and walking in individuals with CP. Visual manipulation of surrounding environment caused increased and variable body sway in individuals with CP compared to their typically developing peers [51]. Further, worsening of crouch stance was observed after removing visual input, thus indicating the dominant role visual input plays in control of standing balance in individuals with CP. With respect to walking, our recent work investigated how individuals with CP use visual input for walking balance control compared to their age-and sex-matched peers by subjecting them to visual sideways fall stimuli while walking in a virtual environment [46]. Our results showed that individuals with CP had a magnified and delayed response to visual perturbations, thus implying that they were more affected by changes in visual input and hence, relied more on vision for walking balance control.

The central nervous system adapts to changes in the environment by continuously adjusting the relative weight of different sensory sources such as vision, proprioception and vestibular system [42]. More reliable sensory inputs are weighed more strongly than less reliable inputs. The ability to upweight (i.e., increase the reliance on) the proprioceptive input as needed, especially in situations where one might receive insufficient or conflicting visual input, e.g., when moving from a well-lit to a dark room, is extremely important in maintaining upright balance. Children with typical development can reweight multisensory inputs from visual and proprioceptive sources from 4-6 years of age onwards [39,51]. They were able to reduce their reliance on vision when receiving visual perturbations of increasing amplitude in standing. Individuals with CP also showed the ability to downweigh vision when large visual perturbations were provided. Thus, there is evidence of sensory reweighing in individuals with CP. Because individuals with CP have impaired proprioception, we postulate that augmenting their proprioception might help them reweight the sensory inputs such that they are able to reduce the reliance on vision, thus showing reduced responses to visual perturbations. Proprioceptive augmentation through vibrotactile cues has reduced the center of mass (CoM) displacement after translational perturbations in standing in healthy young adults [38]. It is not known if children with CP will similarly be able to upweight proprioceptive feedback and show reduced reliance on vision if they receive augmented proprioceptive feedback.

In this study, we augment proprioception by applying a sensory-based modality called stochastic resonance stimulation (SR). SR is a phenomenon where random, sub-sensory noise improves the ability of the sensory system to detect a signal. In patients with impaired proprioception, SR can help make a weak proprioceptive signal more likely to cross the sensory perception threshold and thus become more detectable [26–28]. SR stimulation has improved standing and walking balance in several clinical populations, such as patients with functional ankle instability (FAI) [29,30], diabetic neuropathy, stroke, and in older adults [31,77] In individuals with CP, SR stimulation significantly reduced postural sway in standing [43] and during regular, unperturbed walking [84]. In this study, we investigate whether using

SR to increase the acuity of proprioceptive feedback can be used to address excessive reliance on vision in CP during visually perturbed walking. The typical response to a visual perturbation is to move the body's center of mass (CoM) away from the direction of fall stimulus [54]. Our hypothesis is that by augmenting proprioception, individuals with CP can rely more on proprioception, less on vision and thus show a reduced CoM response to the visual stimulus than without augmenting proprioception. By upweighting proprioceptive input, SR may reduce the dependence on visual input for balance control, thus freeing visual information for high-level use such as navigation and obstacle avoidance.

The two biomechanical mechanisms typically used to modulate lateral CoM movement during walking are: (a) ankle roll, which involves using lateral ankle musculature to bring about inversion at the stance ankle and pull the body to one side, [37,57], and (b) the foot placement, which involves stepping in the direction of a perceived fall to help accelerate the movement of the body away from the fall in subsequent steps [54,56]. Prior work [46] showed that compared to typically developing peers, individuals with CP respond to visual perturbations with reduced ankle roll and increased foot placement change. In this study, we seek to investigate how these underlying biomechanical mechanisms are affected by augmented proprioceptive input through SR. Our hypothesis is that with SR, individuals with CP will show a reduction in ankle roll and foot placement response, which would in turn be the mechanism for the hypothesized decrease in overall CoM response.

The primary aim of this study is to investigate whether SR stimulation reduces the reliance on vision in individuals with CP compared to age- and sex-matched typically developing peers (TD) during visually perturbed walking. We hypothesize that SR stimulation will reduce the CoM responses to visual perturbations compared to the no SR stimulation condition, with greater reduction in the CP group compared to TD. Our secondary hypothesis is that SR stimulation would decrease the ankle roll and foot placement response in the CP group.

4.4 Methods

4.4.1 Participants

We recruited 17 ambulatory individuals with spastic diplegic or hemiplegic CP through advertisements at local hospitals. Seventeen age-matched (± 6 months) and sex-matched typically developing individuals (TD) were recruited through advertisements and social media. Our CP group specifically included individuals with Gross Motor Function Classification (GMFCS levels I-II) to enable completion of the visual perturbation walking protocol without relying on a handrail for tactile cues. All participants were screened by a physical therapist for the inclusion and exclusion criteria listed in Table 4.1.

Table 4.1: Inclusion and Exclusion Criteria

Inclusion	**Exclusion**
• Age 8 - 24 years • Diagnosis of spastic diplegic or hemiplegic CP • GMFCS classification level I or II (ability to walk independently without assistive device) • Visual, perceptual, and cognitive/ communication skills to follow multiple step commands* • Seizure-free or well controlled seizures*	• Diagnosis of athetoid, ataxic or quadriplegic CP • History of selective dorsal root rhizotomy • Botox injections in the lower limb (past 6 months) • Severe spasticity of the lower extremity muscles (e.g., a score of 4 on the Modified Ashworth Scale) • Irreversible muscle contractures

• Ability to communicate pain or discomfort*	• Lower extremity surgery or injuries in the past year* • Visual or vestibular deficits*

We included individuals with both diplegia and hemiplegia in the CP group. To analyze the heterogenous group, we analyzed the data by considering the more affected and less affected sides separately. We determined the more affected side as the one with hemiplegia in individuals with hemiplegic CP, the one self-identified as the more affected side in individuals with diplegic CP and the non-dominant side in the TD group. The TD group self-determined their dominant side as their preferred lower limb of use during daily activities. The University of Delaware Institutional Review Board provided ethical oversight and approved the study protocol, which is registered at clinicaltrials.gov (NCT05233748). Informed parental consent and child assent were obtained.

4.4.2 Instrumentation

Participants walked on a split-belt treadmill with the belts tied to operate synchronously (Bertec Inc., Columbus, Ohio, United States) in a virtual reality domed screen that completely covered their field of vision. The virtual scene comprised a 4-m wide, infinitely long corridor made of floating cubes and a checkered floor (Unity 3d, Unity Technologies, San Francisco, CA, United States). The perspective in the virtual world adapted in real time to the participant's head movement by being linked to two infrared markers on the forehead. The treadmill was user self-paced through a custom labview program (National Instruments Inc., Austin, TX, United States) such that the speed of the treadmill adapted in real time to the participant's self-selected walking speed.

Each visual perturbation or virtual "fall" began at the heelstrike of either foot. A stimulus consisted of rotating the virtual scene around an anterior-posterior axis of the treadmill with an angular acceleration of 45º/s^2 for 600 ms. The scene remained tilted for 2000 ms and then reset to the horizontal over the next 1000 ms with a constant angular velocity. These perturbations mimic the optic flow of falling sideways around the stance foot and have been used extensively in our previous work [37,46,54,67]. The perturbations were triggered at pseudo-randomly selected heel strikes of either foot, where each such trigger was followed by a 10-12 step washout period between the reset of the visual scene and the next trigger. To distinguish the response that was entirely due to visual perturbations from the regular body sway during unperturbed, steady-state walking, we alternated between triggers with an actual perturbation as described above and triggers with no perturbation, i.e., the participant continued walking in a regular, unperturbed manner.

We measured full body kinematics using a 13-camera motion capture system (Qualisys Inc., Gothenberg, Sweden). We used a full body Plug-in Gait marker set [62] with an additional marker on 5th metatarsal head bilaterally and six additional markers on the anterior thigh and shank. We recorded marker data at 200 Hz and ground reaction forces at moments at 1000 Hz. We low pass filtered the force plate data with 4th order Butterworth filter at a cut-off frequency of 20 Hz. We performed inverse kinematics for a 15-segment biomechanical model using OpenSim 4.0 [63]. We further processed the data to compute the below mentioned outcome measures (See section on Outcome Measures) using custom scripts in MATLAB.

4.4.3 SR Stimulation

A custom Labview program was used to generate the SR signal (Uniform White Noise) driving 6 stimulators (STMISOLA, Biopac Systems, Inc., Goleta, USA). SR intensity was defined as the amplitude of the interval of the uniform white noise. We placed self-adhesive electrodes over the ankle (anterior talofibular and deltoid ankle ligaments), shank (lateral soleus and peroneus longus, and tibialis anterior muscles) and at the hip (inferior and posterolateral, respectively, to the greater trochanter to stimulate the hip joint capsule and gluteus medius, and gluteus maximus). The experimental set-up is shown in Figure 4.1.

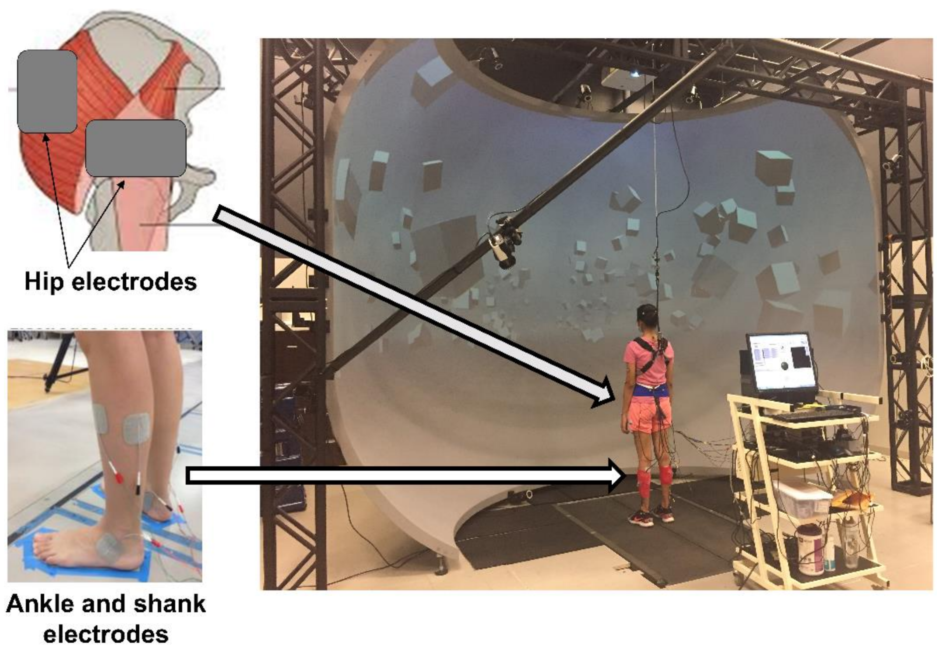

Figure 4.1: Experimental setup with the computer that generated the SR signal and six stimulators that delivered SR stimulation via surface electrodes at the hip, shank, and ankle. The electrode leads were long enough to allow unencumbered walking at self-selected pace on the treadmill and were secured around the shank using a 3M Coban self-adhesive wrap.

4.4.4 Protocol

Participants were given at least two 2-minute practice trials, one without any visual perturbations to get accustomed to the self-pacing treadmill and another 2-minute trial with the visual perturbations to get comfortable with the virtual environment and the visual perturbation.

The experimental protocol included the following steps. Steps 1 and 2 are the same steps under the protocol in the previous chapter. The Step 3 mentioned in the protocol below follows the unperturbed walking protocol (Step 3 of previous chapter).

<u>(1) Determine individual SR Sensory threshold:</u> As a reference value for the range of possible intensities for SR stimulation, we determined each subject's individual sensory detection thresholds at each stimulation site. A sensory threshold was defined as the minimum level of stimulation required for an individual to detect a mild tingling sensation. Participants walked on the treadmill at a self-selected fixed speed while the stimulation intensity was increased in increments of 0.1 mA until the participant reported feeling the sensation. To verify this threshold, we decreased the intensity until the participant could no longer feel the stimulation. We repeated this procedure thrice and the sensory threshold for that site was the lowest stimulation intensity over the three repetitions.

<u>(2) SR Optimal Intensity:</u> For stochastic resonance to boost the detection of proprioceptive signals, a specific optimal level of SR stimulation intensity is required. To find the optimal intensity for each participant, we tested balance performance at 25%, 50%, 75%, and 90% of the participant-specific sensory threshold derived in the previous step. Each participant walked for two minutes at each intensity on the treadmill with rest breaks in between each trial. The SR intensities were presented in randomized order via a computerized protocol. We assessed balance performance for

each intensity by calculating the minimum lateral margin of stability (MOS), a measure previously used for characterizing balance control during walking in children with and without CP [78]. A larger MOS implies a larger impulse is needed to become unstable, and in turn implies higher stability. The SR intensity that is the most protective against a lateral fall i.e., greatest increase in the MOS, among the four SR intensities was defined as the individual's optimal intensity (SRopt) level and used for subsequent testing. Because the SR intensities are sub-threshold, i.e., below 100% of sensory threshold, the participants did not perceive the stimulation and were blinded to the different SR intensities at all times.

(3) Visual Perturbation Protocol: To investigate the effect of SR stimulation on balance, we used SR stimulation at optimal intensity (SRopt) and no stimulation (no SR) as a control condition. Participants completed three trials each of two-minute in length under each of the two (SRopt and noSR) conditions while receiving visual perturbations as described above. The SRopt and noSR conditions were presented in randomized order and the subjects were blinded to either condition.

4.4.5 Outcome Measures

Our primary outcome measure to quantify the effect of SR on response to visual perturbations was the area under the curve of the M-L CoM excursion (AUC M-L CoM excursion). The CoM excursion was defined as the difference between the average CoM for the perturbed steps from control (no perturbation) steps for each participant, which was then integrated over the eight steps following the heel strike that triggered a stimulus. Secondary outcome measures are ankle roll and foot placement responses. We quantified the ankle roll by calculating the subtalar angle at the stance leg, integrated over the first single stance period following the perturbation

(AUC subtalar angle). For the foot placement response, we used the medial-lateral location of the leading foot relative to the trailing foot at heel strike. We first fit a linear model to predict the foot placement from the CoM state at midstance during regular walking [55] and used the difference from this regression line at each step as the outcome measure for foot placement. We then calculated the average foot placement response over the first three post-perturbation steps as a measure of the overall foot placement response following a visual perturbation. These outcome measures have been previously used to assess the response to visual perturbations in individuals with CP [46] and in neurotypical healthy adults [54,67].

4.4.6 Statistical Analysis

Thirty-four participants divided equally over two groups (17 CP, 17 TD) were be recruited. Using significance α=0.05 and power of 0.8, the study was adequately powered to detect a medium effect size (f=0.25).

We performed two-way mixed ANOVAs, with group (CP, TD) as the between subject factor and condition (noSR, SR) as the within-subject factor. We analyzed the more affected and less affected side separately. We assessed assumptions of homoscedasticity and normality, respectively, by Levene's and Shapiro-Wilk tests in addition to visual examination. Between-group differences for baseline characteristics such as age and body mass index (BMI) were assessed using paired samples t-test.

4.5 Results

While participants in both groups were challenged with the visual perturbations, none of the participants stepped off the treadmill or fell over in the safety harness. Out of 34 participants, 31 participants responded to the visual perturbations by moving their CoM away from the direction of virtual fall, which is as expected. However, two participants from the CP group responded by moving their CoM towards the direction of the fall while the third participant responded by moving the CoM vertically lower to the ground rather than moving it in a mediolateral plane. Because these responses are not representative of a group-wide behavior, we chose to exclude these three participants and their corresponding TD controls from the statistical analysis.

The demographic characteristics of both groups are reported in our previously published work [46]. The descriptive statistics for all outcome measures are presented in Supplementary Table 1. The full details of the statistical analysis, including p-values, degrees of freedom and effect sizes are provided in Supplementary Table 2.

4.5.1 Center of Mass response

4.5.1.1 AUC ML CoM excursion

Figure 4.2 shows the average ML CoM excursion over eight post-perturbation steps. Figure 4.3 shows the box and whisker plots for AUC CoM ML excursion. For the more affected side, there was a significant group by condition interaction for AUC ML CoM excursion ($p = 0.005$). Pairwise post hoc comparisons using Bonferroni corrections showed that in the CP group, the average AUC ML CoM excursion reduced significantly with SR compared to the noSR condition ($p < 0.001$), whereas the TD group did not show a significant change with SR compared to noSR ($p = 0.998$). For the less affected side, while both groups seemed to show an increase in the AUC ML CoM excursion, there was no significant effect for condition ($p = 0.111$) nor a group by condition interaction ($p = 0.351$).

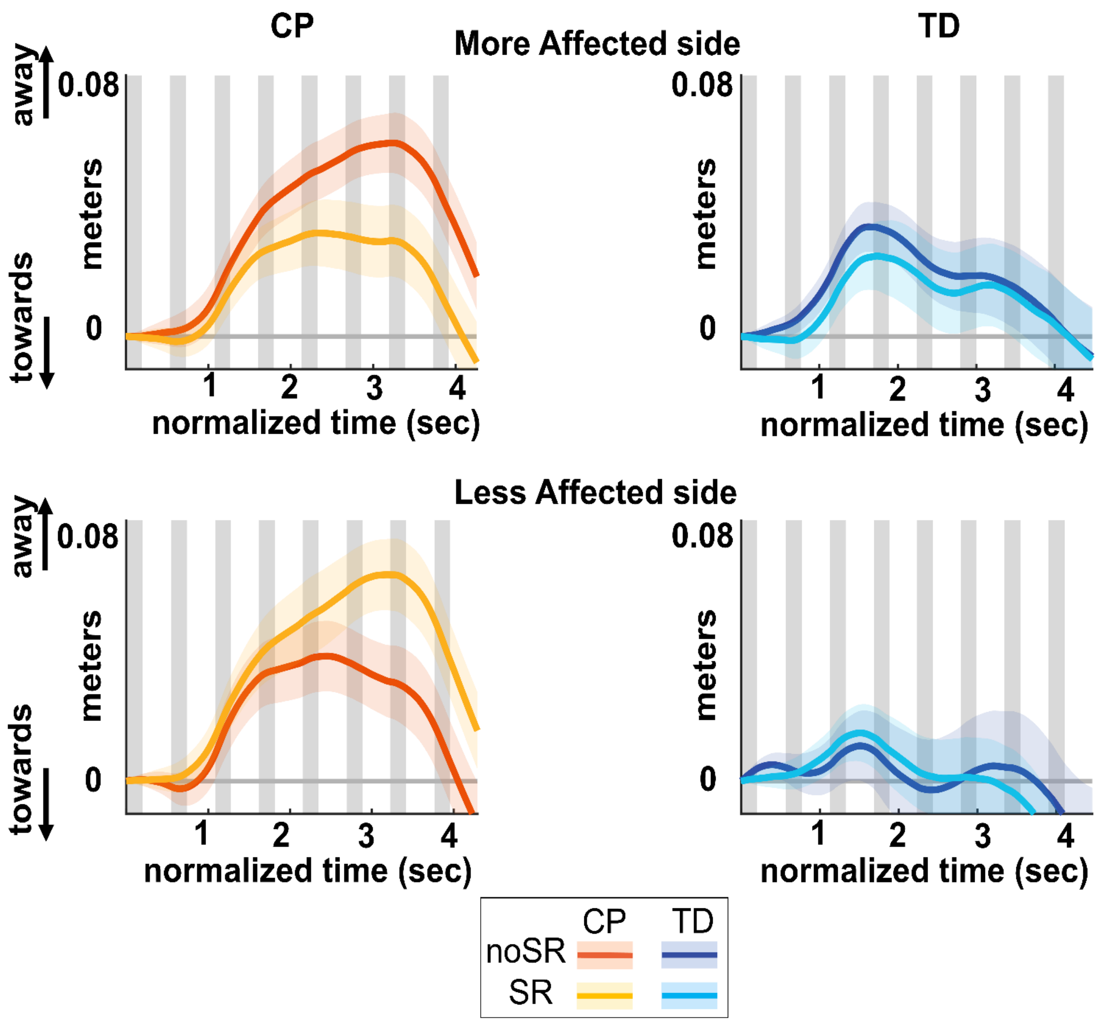

Figure 4.2: Group average trajectories for medio-lateral center of mass excursion in response to visual fall stimuli for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side. Thick gray line along zero at X-axis indicates the mean of control (no fall stimulus) steps, which is subtracted from stimulus data. Shaded areas around each trajectory represent 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with double-stance (gray shading) and single-stance (no shading)

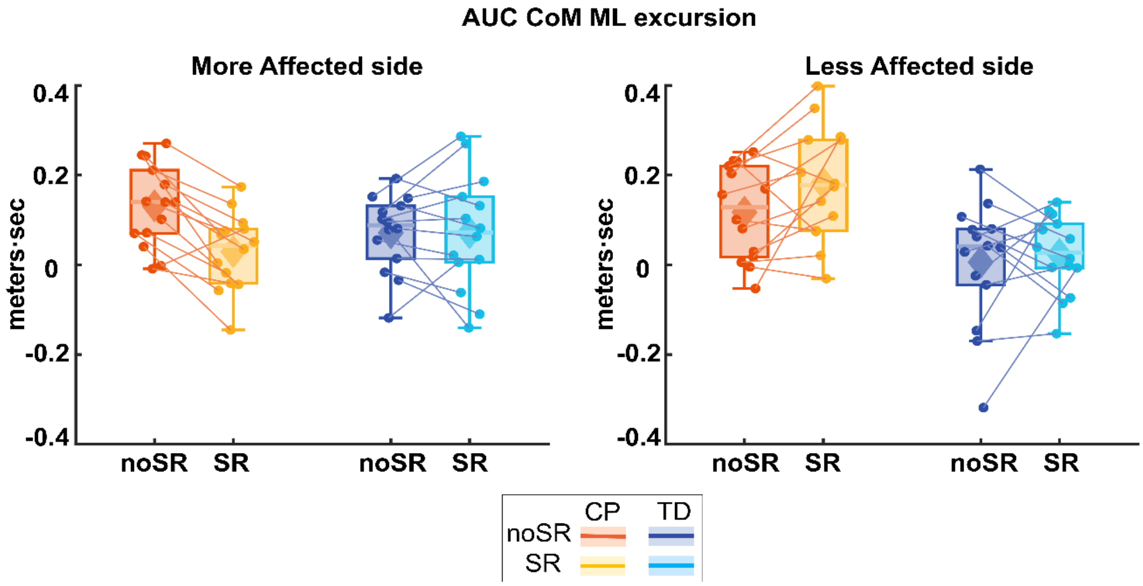

Figure 4.3: Box and whisker plots, with scattered dots indicating each participant for area under the curve of mediolateral center of mass excursion (AUC CoM M-L excursion) for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel).

4.5.1.2 Peak CoM excursion

Figure 4.4 shows the box and whisker plots for peak CoM excursion. For the more affected side, there was a significant group by condition interaction for Peak CoM excursion ($p = 0.010$). Pairwise post hoc comparisons using Bonferroni corrections showed that in the CP group, the average peak excursion reduced significantly with SR compared to the noSR condition ($p < 0.001$), whereas the TD group did not show a significant change with SR compared to noSR ($p = 0.864$). For the less affected side, there was no statistically significant effect for condition ($p = 0.215$) nor a group by condition interaction ($p = 0.070$).

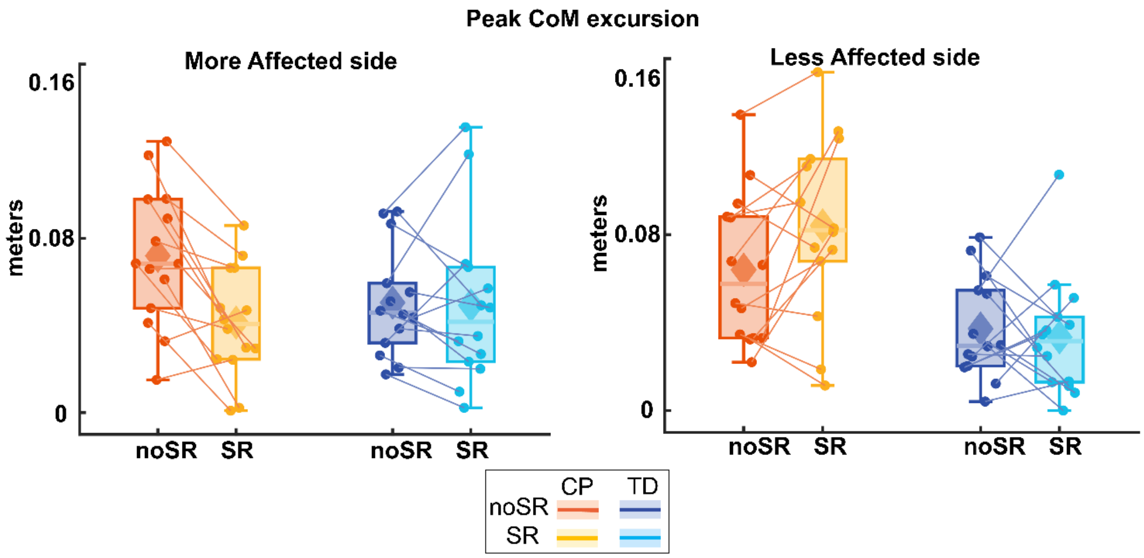

Figure 4.4: Box and whisker plots, with scattered dots indicating each participant for peak center of mass mediolateral excursion (Peak CoM ML excursion) for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side.

4.5.1.3 Peak Time

Figure 4.5 shows the box and whisker plots for peak time. For the more affected side, while the CP group did reduce their peak time by about 600 ms with SR compared to noSR, there was no statistically significant effect for condition (p = 0.070) nor a group by condition interaction (p = 0.216). For the less affected side, CP group increased their peak time with SR compared to noSR, however, there was no significant effect for condition (p = 0.645) nor a group by condition interaction (p = 0.168).

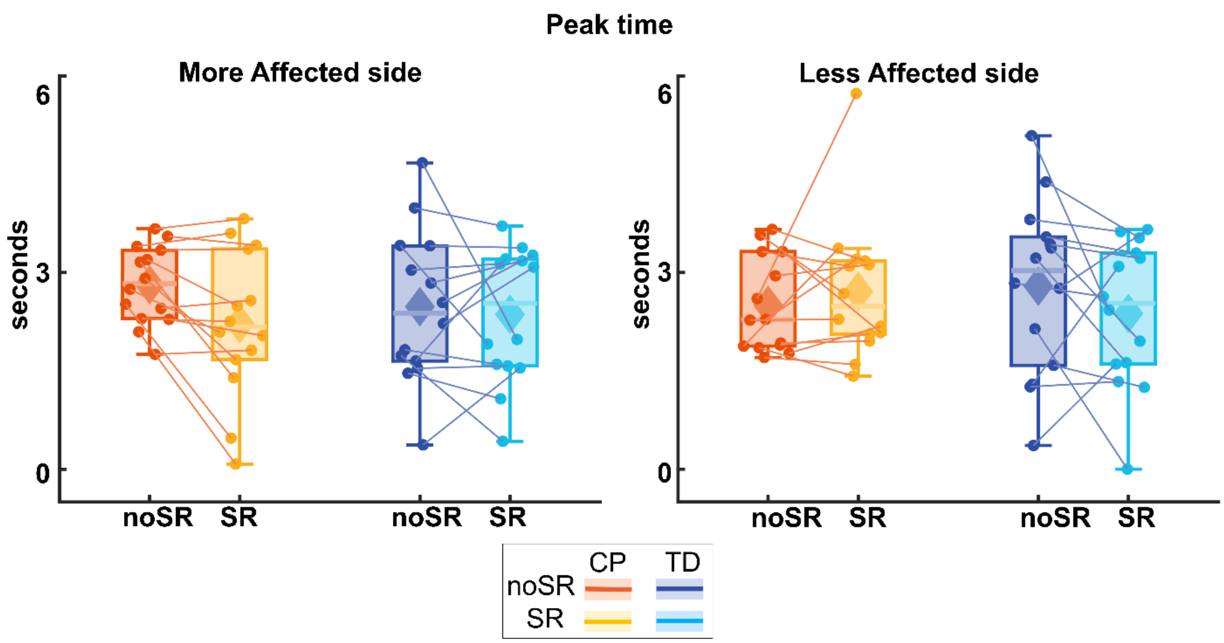

Figure 4.5: Box and whisker plots, with scattered dots indicating each participant for peak time of center of mass mediolateral excursion (Peak Time) for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side.

4.5.2 Ankle roll response

Figure 4.6 shows the average subtalar angle over the first post-perturbation step. Figure 4.7 shows the box and whisker plots for subtalar angle. For the affected side, both groups showed a reduction in the AUC subtalar angle with SR compared to noSR, indicating a reduced ankle inversion or a reduced ankle roll response. However, there was no significant condition effect ($p = 0.317$) nor a group by condition interaction ($p = 0.586$). For the less affected side, there was a significant group by condition interaction ($p = 0.043$). Pairwise post hoc comparisons using Bonferroni corrections showed that in the TD group, the average AUC subtalar angle increased significantly with SR compared to the noSR condition (p = 0.031), whereas the CP group did not show a significant change with SR compared to noSR (p = 0.477).

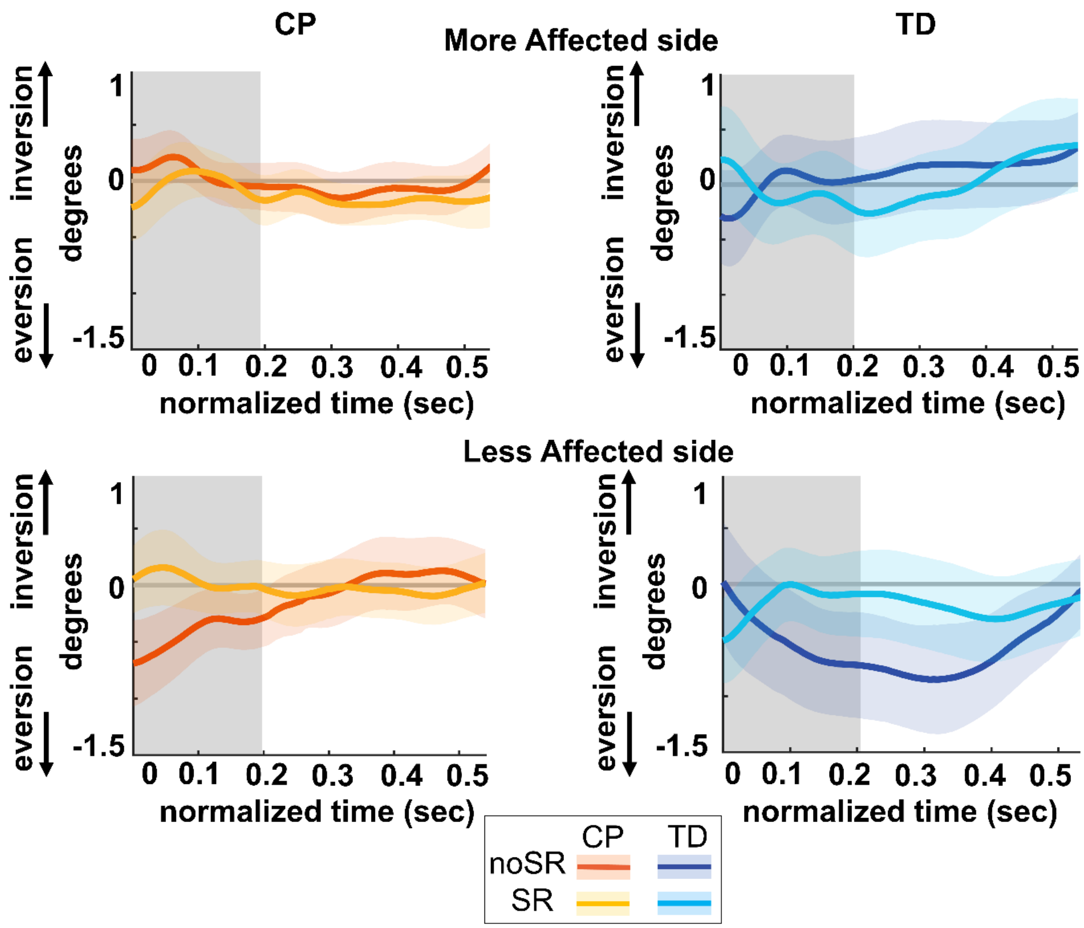

Figure 4.6: Group average trajectories for subtalar angle during the first post-stimulus step following a visual fall perturbation for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side. Thick gray line along zero at X-axis indicates the mean of control (no fall stimulus) steps, which is subtracted from stimulus data. Shaded areas around each trajectory represent 95% confidence interval. X-axis shows 8 steps, time-normalized to 100 timepoints per steps, with double-stance (gray shading) and single-stance (no-shading). Positive and negative Y-axis indicates inversion and eversion, respectively.

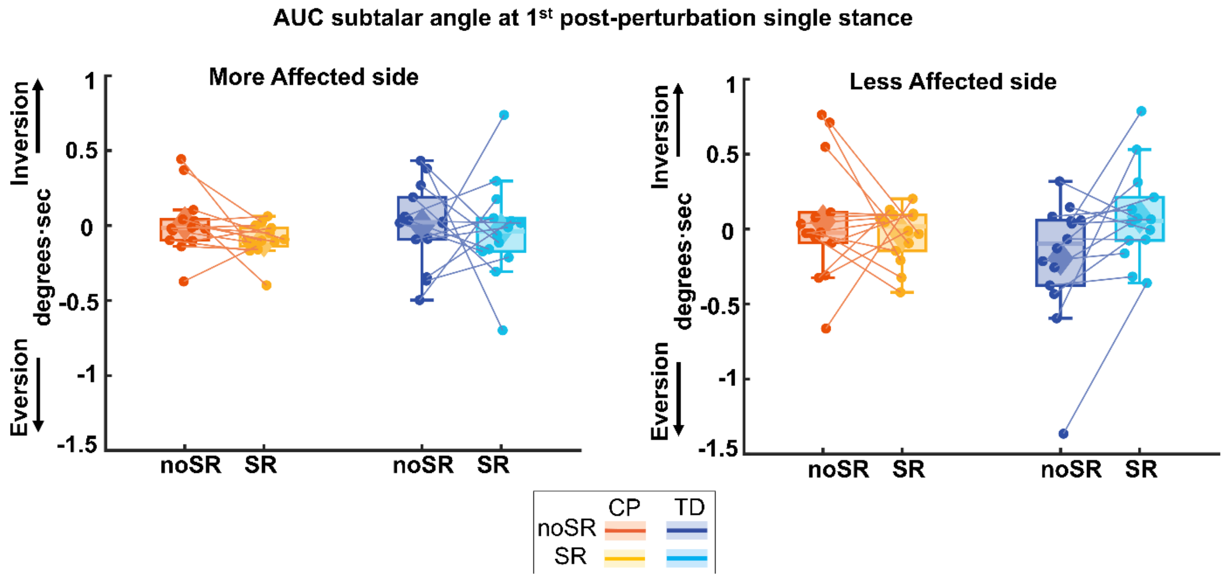

Figure 4.7: Box and whisker plots, with scattered dots indicating each participant, for AUC subtalar angle for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side.

4.5.3 Foot placement response

Figure 4.8 shows the average foot placement over the first three post-perturbation steps.

For the affected side, there was no significant effect for condition ($p = 0.974$) nor a group by condition interaction ($p = 0.820$). Similarly, for the less affected side, there was no significant effect for condition nor a group by condition interaction ($p = 0.844$) nor a significant effect for condition ($p = 0.133$).

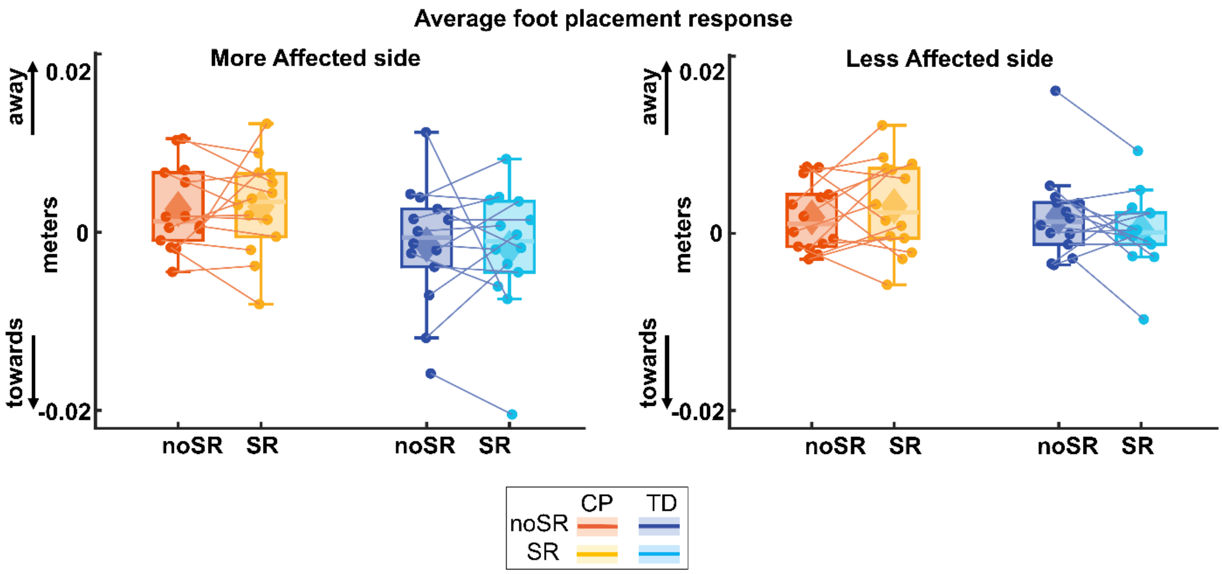

Figure 4.8: Box and whisker plots, with scattered dots indicating each participant, for average foot placement response over first three post-perturbation steps for both noSR and SR conditions in CP (orange: noSR, yellow: SR) and TD (dark blue: noSR, light blue: SR) on the more affected (left panel) and less affected (right panel) side.

4.6 Discussion

In this study, we investigated how the response of individuals with and without CP to visual perturbations changed with application of a sensory-centric therapy such as SR stimulation. As hypothesized, the CP group showed an overall reduced response to the visual perturbations with SR compared to sham stimulation whereas the TD group did not show any change with or without SR. This improvement in the response to visual perturbations was only seen on the more affected side, whereas there was no significant change with or without SR for either group on the less affected side. However, contrary to our hypothesis, the large reduction in the CoM response was not mirrored in the two mechanisms typically responsible for the CoM response, ankle roll and foot placement response. Thus, while our study provides compelling evidence that SR stimulation helped individuals with CP to reduce their response to visual fall stimuli, implying that they were less affected by visual perturbations with SR, the specific mechanisms responsible for the CoM response remain unclear.

Prior work on the response of individuals with CP to visual perturbations compared to their TD peers has shown that they have a magnified and delayed CoM response. With SR stimulation, the CP group reduced their overall CoM response to visual perturbations, as indicated by a reduced AUC for CoM excursion, compared to the perturbation trials without SR on the more affected side. A magnified CoM response during walking and standing in individuals with CP [12,46,51] and during walking in older adults [18] suggests increased reliance on vision over other senses, particularly impaired proprioception, for balance control. Thus, a reduction in the CoM response to visual perturbation suggests a reduced reliance on vision and a potential upweighting of proprioception via SR stimulation. Lastly, the peak CoM excursion, which indicates the magnitude of how far the CoM travelled after a visual perturbation, also showed similar findings as the AUC CoM excursion. The peak time, which is indicative of the delay in generating the peak CoM response, also reduced by ~600 ms with SR. While this difference was not statistically significant, given that the average peak time for the TD group was around 2 seconds, a reduction of this magnitude is critical from a neuromotor control standpoint.

While we found statistically significant improvements in CoM response with SR stimulation on the more affected side, the opposite results, i.e., an increase in the CoM response (though not statistically significant), was observed with SR on the less affected side in both groups. Why is the response so different on the affected vs. the less affected side? One possible explanation is that we selected the optimal SR intensity as the one that resulted in the greatest increase in MoS, i.e., the intensity that best increased the stability, on the more affected side. Although this intensity was selected to optimize balance control on the more affected side, it was applied evenly to perturbations triggered by heelstrikes of either side as part of the randomized protocol. We made these decisions in the protocol design for two reasons. First, based on our prior work that did not show any side-specific differences in the responses to visual perturbations, we did not expect the more and less affected side to behave differently. Second, it was not feasible for the studied pediatric population to repeat the measurements with an intensity selected for optimal effect on the less affected side because it would have made the protocol longer and tiresome, particularly for the younger participants in our cohort. Thus, while this optimal intensity may have been tailored to the more affected side, which is where we expected the most deficits to be present, it may have resulted in too little or too much stimulation for the less affected side. Two studies have specifically investigated the use of different ranges of subthreshold and suprathreshold intensities i.e., intensities below and above the sensory threshold, respectively, for SR stimulation. Severini et al [85] showed that subthreshold SR intensities, such as 70% or 90% of the sensory threshold, improved the postural sway while suprathreshold SR, such as 100% and 130% of the sensory threshold, led to increased postural sway. Cordo et al [27] showed that an inverted U-shaped phenomenon exists with respect to SR, where intensities above and below a certain subject-specific optimal level are not successful in improving the detection of the sensory signal. Both these studies point towards the ineffectiveness of SR if the intensity is not carefully selected to be optimal for the specific task. Thus, overdosing or underdosing on the less affected side may be the reason for the observed worsening of response to visual stimulations with SR stimulation.

A change in the CoM response is expected to be accompanied by a corresponding change in the ankle roll and foot placement response, since these are the balance mechanisms driving the whole-body movement by modulating the force against the ground. Our prior work on responses to visual perturbations has shown that individuals with CP have reduced ankle roll and magnified foot placement response. With SR stimulation, we had expected a reduction in either or both the mechanisms. While the ankle roll response was reduced slightly in both groups, its magnitude was too small to drive such a large corresponding decrease in CoM response. Surprisingly, there was no change in the foot placement mechanism, which is generally considered to be the most effective means of generating a reduction in the CoM response of this magnitude [56]. It is possible that there is a different balance mechanism, which is influenced by SR stimulation in individuals with CP that in turn drives their CoM response. But given the heterogeneity seen in the clinical presentation and in the gait abnormalities in this population, an exploration of alternative balance mechanisms responsible for driving the CoM response is beyond the scope of this paper.

Our study has several limitations to consider while interpreting our results. First, our study investigated only the immediate effects of SR application on the response to visual perturbations. While our results demonstrate the potential of SR in improving walking balance in an acute pre- versus post intervention design, we do not know (1) how long these improvements in balance last for i.e. we explicitly test SR against noSR in a design that temporally interlaces both with each other and if there was a carry-over effect, it would reduce the effect by SR trials carrying over into noSR trials directly after, and (2) whether the improvements can be retained with training program, both of which are important considerations for translating the obtained results in actual patient care. Second, sensory reweighing for balance control also involves a third sensory mode, the vestibular system, in addition to vision and proprioception. To focus on the interplay between two sensory systems our research question probed vision and proprioception, with the goal of allowing participants with CP to reduce their over-reliance on vision by improving information from proprioception. We did not actively manipulate the vestibular system through perturbations or stimulation in this protocol. We also screened out individuals with known history of any vestibular disorders and performed vestibular tests prior to beginning the study protocol to rule out any influence of impaired vestibular system on our results. Our results do not shed light on the role of vestibular contributions to balance control in CP and whether similar upweighting of proprioception would be observed if the vestibular system were experimentally perturbed.

4.7 Conclusion

Overall, our findings indicate that a sensory-centric therapeutic intervention, such as SR stimulation, resulted in reduced responses to visual perturbations in individual with CP compared to their age-and sex-matched peers. We propose that SR, through augmented proprioception, may have led to upweighting of visual input and downweighing of visual input, leading to a reduced reliance on vision for walking balance control. While SR has shown to be potentially effective in improving standing balance previously, these findings highlight the potential of SR in altering the integration and relative contributions of sensory input to actively control balance during walking. However, our current results do not pinpoint the exact balance mechanism that drive the observed improvements in the whole-body response and exploration of alternative balance mechanisms in a clinical population such as CP may be a topic for future research.

4.8 Ethics Approval

All participants signed informed parental consent and child assent approved by the Human Subjects Review Board at the University of Delaware prior to study participation (protocol number 1125634-21).

4.9 Consent for Publication

Written informed consent for publication was obtained.

4.10 Availability of Data and Materials

The data associated with this analysis are available from the corresponding author upon request.

4.11 Conflict of Interest

The authors declare that they have no competing interests.

4.12 Funding

This work was supported in part by the Foundation for Physical Therapy Research Promotion of Doctoral Studies II, American Society of Biomechanics Grant-in-Aid, and the University of Delaware Graduate College through the Unidel Distinguished Graduate Scholar Award. HR was supported by the Parkinson's Foundation (PF-JFA-2036) and the National Science Foundation (NSF CRCNS 1822568) Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors. These funding sources played no role in the design of this study, analysis, interpretation of data, or manuscript writing.

4.13 Author Contributions

AS, HR, and SL: conception and design of the work. AS, MA, and HR: data collection and critical revision. AS, SL, JJ, HR: analysis of data and interpretation. AS: drafting the work. AS, MA, SL, JJ, and HR: revision and final approval of the work. All authors reviewed the main manuscript text and agreed to be accountable for the content of the work.

4.14 Acknowledgements

The authors would like to acknowledge Khushboo Verma for assistance with collecting the data used in this study.

Chapter 5

SUMMARY AND CONCLUSIONS

The overall objective of this dissertation was to probe the role of sensory processing in walking balance in children with CP. To achieve this goal, the specific objectives of this work are to investigate how children with CP use visual input for walking balance control and whether they show sensory reweighting i.e., reduce the reliance on vision and increase the reliance on proprioceptive input upon receiving an augmented sensory regulation. The subsequent paragraphs summarize the key findings and clinical implications of each aim and provide considerations for future directions.

5.1 Aim 1 Summary

Because of proprioceptive deficits, individuals with CP rely more on visual input to control standing balance and during single-plane lower limb movements. Increased visual reliance is associated with increased fall risk, especially in situations where one might not receive reliable visual input. It is not known how individuals with CP use visual information for sensorimotor feedback control during walking, where the biomechanical mechanisms used to maintain upright balance are more complex and the threat to balance is higher. Aim 1 addressed this knowledge gap by investigating how individuals with CP respond to visual perturbations while walking in a virtual reality environment compared to those with typical development (TD). We hypothesized that individuals with CP will demonstrate significantly increased response measured as an increased ML COM excursion than their TD peers (H1). Our results showed that individuals in the CP group had a significantly increased area under the curve (AUC) for ML COM excursion and significantly higher peak COM excursion compared to the TD group, implying that individuals with CP had a magnified response to the visual perturbations, supporting hypothesis H1. While not statistically significant, the CP group also showed a higher peak time compared to the TD group, implying they were slower to respond to the perturbations. Overall, these results imply that the body sway in response to the visual perturbations was magnified and delayed in CP group, implying that they were more affected by changes in visual cues and relied more so on visual information for walking balance control. Additionally, we also probed the differences in balance mechanisms driving the observed COM response, namely, the ankle roll mechanism and the foot placement mechanism, between the CP and TD groups. We found that the CP group showed a significantly reduced ankle roll mechanism, as evidenced by the lack of ankle inversion, and a higher foot placement immediately following the visual perturbations compared to the TD group. These results suggest the presence of a dominant proximal over distal strategy for walking balance control.

5.2 Future Directions for Aim 1

While this dissertation only included individuals with GMFCS levels I-II, it is possible that those with greater impairments, such as GMFCS levels III and up, may present with a different response to visual perturbation. A less burdensome protocol, involving shorter bouts of walking and frequent rest breaks may make it possible to recruit individuals with lower functional mobility. Second, this study only considered how individuals with CP may be compensating for reduced proprioception by perturbing the visual system. Another system that is critical for sensorimotor balance control is the vestibular system. We excluded any individuals with known medical history of vestibular disorders to minimize the possibility of an impaired vestibular system influencing our results. However, our results do not shed light on the role of vestibular system in sensorimotor control of walking balance in individuals with CP. It would be interesting to follow up this experiment with a similar protocol for vestibular perturbations during walking and check if a similarly magnified COM response is obtained in CP compared to the TD group with vestibular perturbations as well. Third, the individuals in the CP group in our cohort walked with higher cadence and shorter step time compared to their TD peers. Such inter-group differences in gait could also contribute to the between group results we observed in our study. Repeating the study protocol with a metronome that forces the two groups to walk with similar cadence or speed may help in answering the question of whether it was the differences in gait that led to the observed results. However, this was beyond the scope of the present study and would be another topic for further investigation.

5.3 Aim 2 Summary

There are currently no interventions that specifically augment sensory feedback and address sensory regulation of gait in CP. While SR stimulation significantly improved postural sway during standing balance in children with CP, the majority of the falls in individuals with CP occur in walking and walking related activities such as turning, bending, and lifting. Because walking is inherently more complex, results in standing may not always apply to walking. Aim 2 addressed this knowledge gap by investigating the immediate effects of SR stimulation on balance control during unperturbed walking through margin of stability in children with CP as compared to children with TD. We hypothesized that SR stimulation during walking will enhance balance control through increased margin of stability, with greater improvements in the CP group compared to the TD group (H2). Our results showed that there were small but statistically significant increase in the medio-lateral and anterior-posterior stability with SR compared to the noSR condition. Further, the step width increased, and the step length decreased significantly with SR compared to the noSR condition. We believe that the changes in the step width and step length were the mechanisms through which the individuals with CP changed their lateral and anterior MOS, respectively. In our study, we interpreted the increase in MOS as an increase in the impulse needed to destabilize the upright body. Thus, an increase in MOS would imply that a larger perturbation or destabilizing external force is needed to cause a fall, and hence, would result in a greater protection against a lateral or anterior fall. However, it is important to note that (a) these changes, despite being statistically significant, are small and hence, their clinical relevance in effectively reducing the fall risk is not yet determined, and (b) while most studies interpret an increase in MOS as an increase in stability, it could be interpreted in more than one way. For example, because the individuals with CP walk with a larger MOS than the TD group, one could argue that the CP group should reduce their MOS after SR to match the walking behavior (i.e., lower MOS) of their TD peers. Also, it is conceivable that SR itself might introduce instability in the sensory system, leading the participants to increase their step width and in turn, their MOS to protect against the instability caused due to SR application. Hence, given the lack of consensus on the interpretation of stability due to a change in MOS and due to a lack of another alternative outcome measure to quantifying walking stability, our results should be interpreted with caution. Thus, we can conclude that SR does lead to a change the lateral and anterior stability, the exact implications for clinical relevance of reducing the fall risk in the CP population is not yet known.

5.4 Future Directions for Aim 2

Similar to the limitation with Aim 1, this study only included high functioning individuals with CP (GMFCS levels I-II). Prior work by others using SR has shown that a greater improvement with SR was associated with greater instability at baseline[81–83]. Thus, including a more impaired cohort may lead to a greater change in walking stability with SR. Further, the central hypothesis behind the use of SR is that application of SR would lead to improved balance and walking function through improved somatosensation at the feet and lower leg. While our results suggest that SR improved walking balance, they do not directly answer the question “Did SR improve the somatosensation along the lower limbs in individuals with CP?”. A future study that investigates the change in somatosensation with and without SR may be able to directly answer the above question. Lastly, measuring a change in the neural activity in the somatosensory cortex with versus without SR to identify the effects of SR on the central nervous system could also be a topic of future research.

5.5 Aim 3 Summary

While children with CP are known to rely heavily on visual information relative to other sensory modes, it is not known if visual reliance can be reduced by providing SR stimulation to increase the acuity of proprioceptive feedback. Thus, by upweighting the proprioceptive input, SR can potentially reduce the reliance on visual input for balance control, freeing visual information for high-level use like navigation and obstacle avoidance. Aim 3 investigated whether SR stimulation, through improved proprioception, reduces responses to visual fall perturbations by decreased M-L COM excursion during walking in children with CP and TD. We hypothesized that SR stimulation will reduce the responses to visual perturbations through decreased M-L COM excursion compared to no SR, with greater reduction in the CP compared to TD.

Our results showed that the CP group showed a significantly reduced AUC COM ML excursion and peak COM excursion with SR compared to the noSR condition, indicating that the overall magnitude of response to perturbations decreased with SR application. Further, the time to peak COM excursion also reduced by around 600 ms in the CP group with SR compared to without SR condition. While this change was not statistically significant, a change of 600 ms is critical from a neuromotor control standpoint, allowing one to respond sooner to a potential threat to balance. These results imply that a sensory-centric intervention, such as SR stimulation, by improving proprioception, may have resulted in downweighing of vision, leading to a reduced reliance on visual input for walking balance. However, there was no significant change in the two balance mechanisms driving the COM response i.e., the ankle roll and foot placement mechanism. Thus, while these results provide evidence of SR lead to large and significant reduction in body sway during visually perturbed walking, the precise balance mechanisms that may be responsible for the reduction in the body sway are not known.

5.6 Future Directions for Aim 3

While we found significantly improved COM response on the affected side with SR application, we found an opposite trend on the less affected side i.e., the response to the visual perturbations that induced a virtual “fall” to the less affected side led to more magnified COM response with SR. A potential explanation for this may be that SR intensity was optimized to improve the MOS on the more affected side. Future studies using SR may want to use a side-specific SR intensity that is customized to optimize the performance separately on each side.

Another critical area of future research would be investigation of the balance mechanisms that drive the COM response in the CP group after receiving SR. Aim 1 showed that the CP group showed a dominant foot placement mechanism to response to visual perturbation. Hence, we expected a reduction in foot placement response to be mechanism underlying the reduced COM response and were surprised with the results that showed no change in it. It is possible that a clinical population such as CP uses other mechanisms, such as trunk lean or COM excursion in the vertical axis, in addition to the above two mechanisms to drive the response to visual perturbations and it is a reduction in this unexplored balance mechanism that was drove the reduction in the COM excursion with SR.

Lastly, this dissertation only looked at the immediate effects of SR on sensorimotor walking balance. Because these results provide compelling evidence that SR can lead to an immediate reduction in the response to visual perturbations, the next step would be to examine if there is a carry-over effect of these improvements and along a more long-term direction, whether these effects can be trained and retained after training.

5.7 Overall Conclusion

Overall, this dissertation establishes the differences in sensorimotor control loops for balance in children with CP and TD, provides proof-of-concept that a sensory-based treatment approach can upweight proprioception and reduce visual reliance for walking balance control. These results will add to the current motor-centric treatments, thus providing a more comprehensive approach to balance rehabilitation. Improved balance will in turn lower incidence of falls and fall-related sequelae, and improve quality of life in children with CP.

REFERENCES

1. Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. *Nat Rev Dis Primers*. 2016;2(1):1-25. doi:10.1038/nrdp.2015.82

2. Jeffries L, Fiss A, McCoy SW, Bartlett DJ. Description of Primary and Secondary Impairments in Young Children With Cerebral Palsy. *Pediatric Physical Therapy*. 2016;28(1):7. doi:10.1097/PEP.0000000000000221

3. Boyer ER, Patterson A. Gait pathology subtypes are not associated with self-reported fall frequency in children with cerebral palsy. *Gait Posture*. 2018;63:189-194. doi:10.1016/j.gaitpost.2018.05.004

4. Morgan P, McDonald R, McGinley J. Perceived Cause, Environmental Factors, and Consequences of Falls in Adults with Cerebral Palsy: A Preliminary Mixed Methods Study. *Rehabil Res Pract*. 2015;2015:196395. doi:10.1155/2015/196395

5. Burton H, Dixit S, Litkowski P, Wingert JR. Functional connectivity for somatosensory and motor cortex in spastic diplegia. *Somatosens Mot Res*. 2009;26(4):90-104. doi:10.3109/08990220903335742

6. Kurz MJ, Heinrichs-Graham E, Arpin DJ, Becker KM, Wilson TW. Aberrant synchrony in the somatosensory cortices predicts motor performance errors in children with cerebral palsy. *J Neurophysiol*. 2014;111(3):573-579. doi:10.1152/jn.00553.2013 [doi]

7. Papadelis C, Ahtam B, Nazarova M, et al. Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study. *Front Hum Neurosci*. 2014;8:725. doi:10.3389/fnhum.2014.00725.

8. Hoon AH, Stashinko EE, Nagae LM, et al. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. *Dev Med Child Neurol*. 2009;51(9):697-704. doi:10.1111/j.1469-8749.2009.03306.x [doi]

9. Kurz MJ, Heinrichs-Graham E, Becker KM, Wilson TW. The magnitude of the somatosensory cortical activity is related to the mobility and strength impairments seen in children with cerebral palsy. *J Neurophysiol*. 2015;113(9):3143-3150. doi:10.1152/jn.00602.2014

10. Damiano DL, Wingert JR, Stanley CJ, Curatalo L. Contribution of hip joint proprioception to static and dynamic balance in cerebral palsy: a case control study. *J Neuroeng Rehabil*. 2013;10(1):57. doi:10.1186/1743-0003-10-57

11. Zarkou A, Lee SCK, Prosser LA, Jeka JJ. Foot and Ankle Somatosensory Deficits Affect Balance and Motor Function in Children With Cerebral Palsy. *Front Hum Neurosci*. 2020;14. doi:10.3389/fnhum.2020.00045

12. Yu Y, Tucker CA, Lauer RT, Keshner EA. Influence of Visual Dependence on Inter-Segmental Coordination during Upright Stance in Cerebral Palsy. *J Mot Behav*. 2020;52(3):249-261. doi:10.1080/00222895.2019.1610860

13. Lee SC. Relationship of visual dependence to age, balance, attention, and vertigo. *J Phys Ther Sci*. 2017;29(8):1318-1322. doi:10.1589/jpts.29.1318

14. Lord SR, Webster IW. Visual Field Dependence in Elderly Fallers and Non-Fallers. *The International Journal of Aging and Human Development*. 1990;31(4):267-277. doi:10.2190/38MH-2EF1-E36Q-75T2

15. Suárez H, Musé P, Suárez A, Arocena M. Assessment of the risk of fall, related to visual stimulation, in patients with central vestibular disorders. *Acta Otolaryngol*. 2001;121(2):220-224. doi:10.1080/000164801300043587

16. Wingert JR, Burton H, Sinclair RJ, Brunstrom JE, Damiano DL. Joint-position sense and kinesthesia in cerebral palsy. *Arch Phys Med Rehabil*. 2009;90(3):447-453. doi:10.1016/j.apmr.2008.08.217

17. Slaboda JC, Lauer RT, Keshner EA. Postural Responses of Adults With Cerebral Palsy to Combined Base of Support and Visual Field Rotation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. 2013;21(2):218-224. doi:10.1109/TNSRE.2013.2246583

18. Franz JR, Francis CA, Allen MS, O'Connor SM, Thelen DG. Advanced age brings a greater reliance on visual feedback to maintain balance during walking. *Hum Mov Sci*. 2015;40:381-392. doi:10.1016/j.humov.2015.01.012

19. Blumetti FC, Wu JCN, Bau KV, et al. Orthopedic surgery and mobility goals for children with cerebral palsy GMFCS level IV: what are we setting out to achieve? *J Child Orthop*. 2012;6(6):485-490. doi:10.1007/s11832-012-0454-7

20. Dreher T, Wolf SI, Maier M, et al. Long-term results after distal rectus femoris transfer as a part of multilevel surgery for the correction of stiff-knee gait in spastic diplegic cerebral palsy. *J Bone Joint Surg Am*. 2012;94(19):e142(1-10). doi:10.2106/JBJS.K.01300

21. Pin T, Dyke P, Chan M. The effectiveness of passive stretching in children with cerebral palsy. *Dev Med Child Neurol*. 2006;48(10):855-862. doi:10.1017/S0012162206001836

22. Taylor NF, Dodd KJ, Baker RJ, Willoughby K, Thomason P, Graham HK. Progressive resistance training and mobility-related function in young people with cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol*. 2013;55(9):806-812. doi:10.1111/dmcn.12190

23. Riquelme I, Zamorano A, Montoya P. Reduction of Pain Sensitivity After Somatosensory Therapy in Adults with Cerebral Palsy. *Front Hum Neurosci*. 2013;7. doi:10.3389/fnhum.2013.00276

24. Trivedi R, Gupta RK, Shah V, et al. Treatment-induced plasticity in cerebral palsy: a diffusion tensor imaging study. *Pediatr Neurol*. 2008;39(5):341-349. doi:10.1016/j.pediatrneurol.2008.07.012

25. Hanggi P. Stochastic Resonance in Biology How Noise Can Enhance Detection of Weak Signals and Help Improve Biological Information Processing. *Chemphyschem*. 2002;3:285-290. doi:10.1002/1439-7641(20020315)3:3<285::AID-CPHC285>3.0.CO;2-A

26. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. *Nature*. 1996;383(6603):770. doi:10.1038/383770a0

27. Cordo P, Inglis JT, Verschueren S, et al. Noise in human muscle spindles. *Nature*. 1996;383(6603):769-770. doi:10.1038/383769a0

28. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. *Clin Neurophysiol*. 2004;115(2):267-281.

29. Ross SE, Guskiewicz KM. Effect of Coordination Training With and Without Stochastic Resonance Stimulation on Dynamic Postural Stability of Subjects With Functional Ankle Instability and Subjects With Stable Ankles. *Clinical Journal of Sport Medicine*. 2006;16(4). https://journals.lww.com/cjsportsmed/Fulltext/2006/07000/Effect_of_Coordination_Training_With_and_Without.7.aspx

30. Ross SE, Linens SW, Wright CJ, Arnold BL. Customized Noise-Stimulation Intensity for Bipedal Stability and Unipedal Balance Deficits Associated With Functional Ankle Instability. *J Athl Train*. 2013;48(4):463-470. doi:10.4085/1062-6050-48.3.12

31. Priplata AA, Patritti BL, Niemi JB, et al. Noise-enhanced balance control in patients with diabetes and patients with stroke. *Ann Neurol*. 2006;59(1):4-12. doi:10.1002/ana.20670

32. Gravelle DC, Laughton CA, Dhruv NT, et al. Noise-enhanced balance control in older adults. *Neuroreport*. 2002;13(15):1853-1856. doi:10.1097/00001756-200210280-00004

33. Galica AM, Kang HG, Priplata AA, et al. Subsensory vibrations to the feet reduce gait variability in elderly fallers. *Gait Posture*. 2009;30(3):383-387. doi:10.1016/j.gaitpost.2009.07.005

34. Lipsitz LA, Lough M, Niemi J, Travison T, Howlett H, Manor B. A shoe insole delivering subsensory vibratory noise improves balance and gait in healthy elderly people. *Arch Phys Med Rehabil*. 2015;96(3):432-439. doi:10.1016/j.apmr.2014.10.004

35. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. *Nature*. 1996;383(6603):770. doi:10.1038/383770a0

36. Kyvelidou A, Harbourne RT, Willett SL, Stergiou N. Sitting postural control in infants with typical development, motor delay, or cerebral palsy. *Pediatr Phys Ther*. 2013;25(1):46-51. doi:10.1097/PEP.0b013e318277f157

37. Reimann H, Fettrow T, Jeka J. Strategies for the Control of Balance During Locomotion. *Kinesiology Review*. 2018;7:1-8. doi:10.1123/kr.2017-0053

38. Ma CZH, Lee WCC. A wearable vibrotactile biofeedback system improves balance control of healthy young adults following perturbations from quiet stance. *Hum Mov Sci*. 2017;55:54-60. doi:https://doi-org.udel.idm.oclc.org/10.1016/j.humov.2017.07.006

39. Bair WN, Kiemel T, Jeka JJ, Clark JE. Development of multisensory reweighting for posture control in children. *Exp Brain Res*. 2007;183(4):435-446. doi:10.1007/s00221-007-1057-2 [doi]

40. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing*. 2006;35 Suppl 2:ii7-ii11. doi:10.1093/ageing/afl077

41. Mergner T, Rosemeier T. Interaction of vestibular, somatosensory and visual signals for postural control and motion perception under terrestrial and microgravity conditions–a conceptual model. *Brain Res Brain Res Rev*. 1998;28(1-2):118-135. doi:10.1016/s0165-0173(98)00032-0

42. Peterka RJ. Sensorimotor integration in human postural control. *J Neurophysiol*. 2002;88(3):1097-1118. doi:10.1152/jn.2002.88.3.1097

43. Zarkou A, Lee SCK, Prosser LA, Hwang S, Jeka J. Stochastic resonance stimulation improves balance in children with cerebral palsy: a case control study. *J Neuroeng Rehabil*. 2018;15(1):115. doi:10.1186/s12984-018-0467-7

44. Moss F, Milton JG. Medical technology: balancing the unbalanced. *Nature*. 2003;425(6961):911-912. doi:10.1038/425911a

45. Arvin M, Hoozemans MJM, Pijnappels M, Duysens J, Verschueren SM, van Dieën H. J. Where to Step? Contributions of Stance Leg Muscle Spindle Afference to Planning of Mediolateral Foot Placement for Balance Control in Young and Old Adults. *Front Physiol*. 2018;9:1134. doi:10.3389/fphys.2018.01134

46. Sansare A, Arcodia M, Lee SCK, Jeka J, Reimann H. Individuals with cerebral palsy show altered responses to visual perturbations during walking. *Front Hum Neurosci*. 2022;16. doi:10.3389/fnhum.2022.977032

47. Roncesvalles MN, Woollacott MW, Burtner PA. Neural factors underlying reduced postural adaptability in children with cerebral palsy. doi:10.1097/01.wnr.0000048024.40536.9d

48. Chen J, Woollacott MH. Lower extremity kinetics for balance control in children with cerebral palsy. *J Mot Behav*. 2007;39(4):306-316. doi:10.3200/JMBR.39.4.306-316

49. Crenshaw JR, Petersen DA, Conner BC, et al. Anteroposterior balance reactions in children with spastic cerebral palsy. *Dev Med Child Neurol*. 2020;62(6):700-708. doi:https://doi.org/10.1111/dmcn.14500

50. Tracy JB, Petersen DA, Pigman J, et al. Dynamic stability during walking in children with and without cerebral palsy. *Gait Posture*. 2019;72:182-187. doi:10.1016/j.gaitpost.2019.06.008

51. Barela JA, Focks GMJ, Hilgeholt T, Barela AMF, de P. Carvalho R, Savelsbergh GJP. Perception-action and adaptation in postural control of children and adolescents with cerebral palsy. *Res Dev Disabil*. 2011;32(6):2075-2083. doi:10.1016/j.ridd.2011.08.018

52. Lidbeck C, Bartonek Å, Yadav P, et al. The role of visual stimuli on standing posture in children with bilateral cerebral palsy. *BMC Neurol*. 2016;16(1):1-9. doi:10.1186/s12883-016-0676-2

53. Sonksen PM, Dale N. Visual impairment in infancy: impact on neurodevelopmental and neurobiological processes. *Dev Med Child Neurol*. 2002;44(11):782-791. doi:10.1017/S0012162201002936

54. Reimann H, Fettrow T, Thompson ED, Jeka JJ. Neural Control of Balance During Walking. *Front Physiol*. 2018;9. doi:10.3389/fphys.2018.01271

55. Wang Y, Srinivasan M. Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biol Lett*. 2014;10(9):20140405. doi:10.1098/rsbl.2014.0405

56. Van Dieën JH, Bruijn SM. Control of human gait stability through foot placement. doi:10.1098/rsif.2017.0816

57. Hof AL, Duysens J. Responses of human ankle muscles to mediolateral balance perturbations during walking. *Hum Mov Sci*. 2018;57:69-82. doi:10.1016/J.HUMOV.2017.11.009

58. Reimann H, Fettrow TD, Thompson ED, Agada P, McFadyen BJ, Jeka JJ. Complementary mechanisms for upright balance during walking. *PLoS One*. 2017;12(2):e0172215. doi:10.1371/journal.pone.0172215

59. Burtner PA, Woollacott MH, Qualls C. Stance balance control with orthoses in a group of children with spastic cerebral palsy. *Dev Med Child Neurol*. 1999;41(11):748-757. doi:10.1017/S0012162299001516

60. Palisano R, Rosenbaum PL, Russell D, Galuppi BE. Development and reliability of a system to classify gross motor function in children with Cerebral Palsy The ICF for Parents (P-ICF) View project Autism Classification System of Functioning: Social Communication (ACSF:SC) algorithm study View project. *Article in Developmental Medicine & Child Neurology*. Published online 1997. doi:10.1111/dmcn.1997.39.issue-4

61. Fettrow T, Reimann H, Grenet D, et al. Interdependence of balance mechanisms during bipedal locomotion. *PLoS One*. 2019;14(12):e0225902. doi:10.1371/journal.pone.0225902

62. Davis RB, Õunpuu S, Tyburski D, Gage JR. A gait analysis data collection and reduction technique. *Hum Mov Sci*. 1991;10(5):575-587. doi:10.1016/0167-9457(91)90046-Z

63. Lu TW, O'Connor JJ. Bone position estimation from skin marker co-ordinates using global optimisation with joint constraints. *J Biomech*. 1999;32(2):129-134. doi:10.1016/S0021-9290(98)00158-4

64. Fettrow T, Reimann H, Grenet D, et al. Interdependence of balance mechanisms during bipedal locomotion. *PLoS One*. 2019;14(12):e0225902. doi:10.1371/journal.pone.0225902

65. Vlutters M, van Asseldonk EHF, van der Kooij H. Center of mass velocity-based predictions in balance recovery following pelvis perturbations during human walking. *Journal of Experimental Biology*. 2016;219(10):1514-1523. doi:10.1242/jeb.129338

66. Slaboda JC, Lauer RT, Keshner EA. Continuous visual field motion impacts the postural responses of older and younger women during and after support surface tilt. *Exp Brain Res*. 2011;211(1):87-96. doi:10.1007/s00221-011-2655-6

67. Fettrow T, Reimann H, Grenet D, Crenshaw J, Higginson J, Jeka J. Walking Cadence Affects the Recruitment of the Medial-Lateral Balance Mechanisms. *Front Sports Act Living*. 2019;1. doi:10.3389/fspor.2019.00040

68. Philip SS, Guzzetta A, Chorna O, Gole G, Boyd RN. Relationship between brain structure and Cerebral Visual Impairment in children with Cerebral Palsy: A systematic review. *Res Dev Disabil*. 2020;99:103580. doi:10.1016/J.RIDD.2020.103580

69. Ego A, Lidzba K, Brovedani P, et al. DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY Visual-perceptual impairment in children with cerebral palsy: a systematic review DTVP Developmental Test of Visual Perception PCT Wechsler Intelligence Scale for Children-Revised Picture Com-pletion Subtest Task TVPS Test of Visual Perceptual Skills VPI Visual-perceptual impairment. Published online 2015. doi:10.1111/dmcn.12687

70. VerMaas JR, Embury CM, Hoffman RM, Trevarrow MP, Wilson TW, Kurz MJ. Beyond the eye: Cortical differences in primary visual processing in children with cerebral palsy. *Neuroimage Clin*. 2020;27:102318. doi:10.1016/J.NICL.2020.102318

71. VerMaas JR, Gehringer JE, Wilson TW, Kurz MJ. Children with cerebral palsy display altered neural oscillations within the visual MT/V5 cortices. *Neuroimage Clin*. 2019;23:101876. doi:10.1016/J.NICL.2019.101876

72. Bateni H, Maki BE. Assistive devices for balance and mobility: Benefits, demands, and adverse consequences. *Arch Phys Med Rehabil*. 2005;86(1):134-145. doi:10.1016/J.APMR.2004.04.023

73. Auld ML, Boyd RN, Moseley GL, Ware RS, Johnston LM. Impact of tactile dysfunction on upper-limb motor performance in children with unilateral cerebral palsy. *Arch Phys Med Rehabil*. 2012;93(4):696-702. doi:10.1016/j.apmr.2011.10.025 [doi]

74. Clayton K, Fleming JM, Copley J. Behavioral Responses to Tactile Stimuli in Children with Cerebral Palsy. Published online 2009. doi:10.1080/J006v23n01_04

75. Mclaughlin JF, Felix SD, Nowbar S, Ferrel A, Bjornson K, Hays RM. Pediatric Rehabilitation Lower extremity sensory function in children with cerebral palsy Lower extremity sensory function in children with cerebral palsy. *Pediatr Rehabil*. 2009;8(1):45-52. doi:10.1080/13638490400011181

76. Ross SE, Linens SW, Wright CJ, Arnold BL. Customized Noise-Stimulation Intensity for Bipedal Stability and Unipedal Balance Deficits Associated With Functional Ankle Instability. *J Athl Train*. 2013;48(4):463-470. doi:10.4085/1062-6050-48.3.12

77. Gravelle DC, Laughton CA, Dhruv NT, et al. Noise-enhanced balance control in older adults. *Neuroreport*. 2002;13(15):1853-1856. doi:10.1097/00001756-200210280-00004

78. Tracy JB, Petersen DA, Pigman J, et al. Dynamic stability during walking in children with and without cerebral palsy. *Gait Posture*. 2019;72:182-187. doi:10.1016/j.gaitpost.2019.06.008

79. Hof AL, Gazendam MGJ, Sinke WE. The condition for dynamic stability. *J Biomech*. 2005;38(1):1-8. doi:10.1016/j.jbiomech.2004.03.025

80. Tracy JB, Petersen DA, Pigman J, et al. Dynamic stability during walking in children with and without cerebral palsy. *Gait Posture*. 2019;72:182-187. doi:10.1016/J.GAITPOST.2019.06.008

81. Bassiri Z, Austin C, Cousin C, Martelli D. Subsensory electrical noise stimulation applied to the lower trunk improves postural control during visual perturbations. *Gait Posture*. 2022;96:22-28. doi:https://doi.org/10.1016/j.gaitpost.2022.05.010

82. Acuña SA, Zunker JD, Thelen DG. The effects of sub-threshold vibratory noise on visuomotor entrainment during human walking and standing in a virtual reality environment. *Hum Mov Sci*. 2019;66:587-599. doi:10.1016/J.HUMOV.2019.06.009

83. Aboutorabi A, Arazpour M, Bahramizadeh M, Farahmand F, Fadayevatan R. Effect of vibration on postural control and gait of elderly subjects: a systematic review. *Aging Clin Exp Res*. 2018;30(7):713-726. doi:10.1007/s40520-017-0831-7

84. Ashwini Sansare, Hendrik Reimann, Jeremy Crenshaw, Maelyn Arcodia, Khushboo Verma, Samuel C.K. Lee. Subthreshold electrical noise alters walking balance control in individuals with cerebral palsy. *Gait Posture*. 2023;Under Review.

85. Severini G, Delahunt E. Effect of noise stimulation below and above sensory threshold on postural sway during a mildly challenging balance task. *Gait Posture*. 2018;63:27-32. doi:10.1016/J.GAITPOST.2018.04.031

Appendix A

JOURNAL PERMISSSIONS

Permission to include published manuscript associated with Aim 1/Chapter 2:

Sansare A, Arcodia M, Lee SCK, Jeka J, Reimann H. Individuals with cerebral palsy show altered responses to visual perturbations during walking. Front Hum Neurosci. 2022 Sep 8;16:977032. doi: 10.3389/fnhum.2022.977032. PMID: 36158616; PMCID: PMC9493200.

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Appendix B

INSTITUTIONAL REVIEW BOARD APPROVAL

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

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DATE:	March 14, 2018
TO:	John Jeka, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1125634-3] Neuromotor Control during Walking in Children with Cerebral Palsy
SUBMISSION TYPE:	Revision
ACTION:	APPROVED
APPROVAL DATE:	March 14, 2018
EXPIRATION DATE:	January 16, 2019
REVIEW TYPE:	Full Committee Review
REVIEW CATEGORY:	Subpart D Determination 45 CFR 46.404

Thank you for your submission of Revision 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.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.