Influence of Aging and Neuromodulation-Enhanced Training on Sensorimotor Regulation of Gait and Balance

By

Carrie A. Francis

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

(Biomedical Engineering)

at the

UNIVERSITY OF WISCONSIN-MADISON

2016

Date of final oral examination: May 16, 2016

This dissertation is approved by the following members of the Final Oral Committee:
Darryl G. Thelen, Professor, Mechanical Engineering
Neil C. Binkley, Professor, Medicine
Bryan C. Heiderscheit, Professor, Orthopedics and Rehabilitation
Justin Williams, Professor, Biomedical Engineering
Peter L. E. van Kan, Associate Professor, Kinesiology

# Abstract

Approximately one in three adults over 65 fall annually, with the majority of these falls occurring during locomotion. The underlying causes of these falls could include a number of physiological factors such as age-related declines in sensory acuity, executive function, cognitive capacity, muscle strength and reaction time. Prior studies have identified links between gait variability metrics, dynamic balance and fall risk in older adults. Step width variability is particularly relevant given the inherent challenge in modulating step width to maintain medio-lateral balance during walking. However, challenging walking tasks may be required to elucidate increases in gait variability that arise from subtle age-related changes in cognitive processing and sensorimotor function. This dissertation investigated how visual, cognitive and physical challenges can affect gait variability and muscle coordination in healthy old adults.

The first study investigated the relative effects of perturbed visual feedback, increased cognitive load, and narrowed step width demands on gait variability in healthy old and young adults. Eleven healthy old (OA, average age 71.2 ± 4.2 years) and twelve healthy young (YA, 23.5 ± 3.9 years) adults walked on a treadmill while watching a speed-matched virtual hallway. Subjects walked 1) normally, 2) with medio-lateral visual perturbations, 3) while performing a cognitive task (serial seven subtractions), and 4) with narrowed step width. Motion capture was used to track step width and length over three minutes of walking for each condition. Old subjects were most sensitive to the visual perturbations, with step width variability increasing more than 150% relative to the normal condition. The cognitive

task and walking with narrowed step width did not show any effect on step width or length variability in either group. The dramatic increase in step width variability when old adults were subjected to medio-lateral visual perturbations was likely due to an increased reliance on visual feedback for assessing whole body position with aging.

The second study investigated how old adults modulate lower extremity muscle coordination patterns when presented with challenging walking tasks. It was hypothesized that old adults would have greater muscle co-activation than in young adults in normal, unperturbed walking. Further, it was hypothesized that old adults would increase their use of a co-activation strategy to stiffen joints in walking tasks that challenge balance. Electromyographic (EMG) activity was recorded bilaterally from the medial hamstring (MH), vastus lateralis (VL), medial gastrocnemius (MG), soleus (SL), and tibialis anterior (TA) muscles. Muscle co-activation for MH-VL, MG-TA, and SL-TA pairs were computed. In contrast to some prior studies, old adults in this study exhibited muscle activation patterns that were generally similar to young adults during normal walking at self-selected speed. However, the visual perturbation condition significantly increased muscle co-activation in the old adults, both in comparison to normal walking and relative to young adults. It was concluded that aging is associated with an increased reliance on visual information to maintain balance during walking, with inaccurate visual information causing old adults to adapt their coordination to accommodate the perceived threat to balance.

The final study investigated a noninvasive neuromodulation approach for enhancing gait and balance in old adults. There remains a substantial need for effective balance training programs given the substantial medical and personal costs associated with fall-related injuries. Prior studies have shown that traditional exercise programs can enhance strength in old adults, but that these improvements generally don't translate to improved balance and reduced fall risk. This finding would suggest that deficits in sensory function and sensorimotor integration may be better targets for enhancing balance in old adults. Cranial nerve non-invasive neuromodulation (CN-NINM) is a relatively new technology for enhancing neu-

roplasticity, which in turn could improve sensorimotor processes. CN-NINM uses electrical stimulation of cranial nerve endings in the dorsal surface of the tongue to heighten activity in the brainstem. Prior studies suggest that coupling CN-NINM with gait and balance training may enhance the therapeutic benefits in subjects with traumatic brain injury and multiple sclerosis compared to standard gait and balance therapy. A pilot study of the efficacy of CN-NINM for training gait and balance in old adults was performed. Sixteen old adults (ages 66-80) participated in a double-blind randomized, controlled study. All subjects participated in a 10-day supervised gait and balance training intervention. Half of the subjects (active group) performed the intervention exercises with an active CN-NINM device, while half used a device that delivered only sub-sensory stimulation. Clinical and quantitative assessments of gait variability and postural balance were performed before and after the 10-day intervention. There were significant improvements in gait and balance metrics after training. After the intervention, subjects exhibited reduced step width variability when subjected to visual perturbations during walking. Further there were some reductions in standing sway measures. However, there were no significant differences in post-training metrics between the active and control groups. It is noted that the subjects who participated were generally healthy and physically active with limited history of falling. Future studies should consider the potential benefits of CN-NINM in old adults with a history of falls, given their greater potential for improvement.

# Acknowledgements

I would like to take the time to thank the following people and funding sources.

First, I want to thank my adviser, Darryl Thelen for letting me join the lab somewhat last-minute and helping me find funding as a new grad student. Thank you also for your support and encouragement throughout graduate school, both academically and with my extra-curricular activities.

I would like to acknowledge the other members of my committee for their time, feedback, direction, and encouragement throughout this process.

Thank you to Amy Lenz for assisting with my master's project and helping me get acclimated to the lab and Madison. Your friendship has been greatly appreciated. Thank you also to Laura Slane and Rachel Lenhart for your friendship, mutual support, and lab social committee organization through grad school. Thank you to Jason Franz for help with data collection and providing feedback on numerous drafts of various sorts. I also want to acknowledge Holly Schoenberg, Mike Schmidt, Kristen Rasske, and Samuel Acuña for their assistance with collecting the data herein. Thank you to Mikel Stiffler, Christa Wille, and Liz Chumanov for assistance with the motion capture lab. Thank you also to the other members of NMBL and BJB, past and present, for your friendship and willingness to be guinea pigs.

Thank you to the Tactile Communications and Neurorehabilitation Lab for letting me take on this project. Thank you especially to Kim Skinner for training me to implement the CN-NINM approach, providing feedback and guidance when I had questions, and helping with DGI evaluations. Thank you also to Janet Ruhland and Georgia Corner for helping with DGI evaluations.

Thank you to my parents, Steve and Judy Francis. I would not be the person I am today without your unconditional love and constant support. Thank you for never telling me I had limits and giving me such a wide range of skill sets and opportunities to try new things.

Thank you to the Blackhawk Church volleyball group for keeping me (somewhat) sane through this process. I am grateful to Ryan Van Hoveln, Stephen and Joy Block, Luisa Meyer, and Isaac Portz for good conversations and friendship both over meals and from a distance. Thanks to the philosopher-chemists (i.e. Cale Weatherly and Josh Carr) for being a core group of guests for dinner parties (if you feed them they will come, as long as the meal is after 7pm on Saturday or on a Sunday). Thank you also to the members the InterVarsity Graduate Christian Fellowship for challenging me to think more deeply about my faith while we dive into the nuances of our respective academic fields, especially Mary van Vleet, Linda Park, LieNa Tan, Chris and Kate Stutz, and Emily Voigt. Thank you for providing a solid community and support network through this journey.

Thank you to Jane Matlock and Sherry Shelley for inspiring me as a middle schooler and giving me the opportunity to be a guest scientist in my hometown.

I also acknowledge the individuals who participated in the studies described herein, without your willingness to show up day in and day out for evaluations and daily training (some would say torture), this thesis would not have been possible.

I would also like to thank Paul Rebillot and Scott Hughes for first encouraging me to pursue a Ph.D. (read: for getting me into this!).

I would like to acknowledge Mary Kay Strauss and Amy Nichols for inspiring me to pursue Biomedical Engineering.

Through my time in graduate school, I have been funded by NIH grants: T90 DK070079, AR057136, T32 EB114342, and F31AG046945. I also received funding from the Flynn Fund and the UW Center for Rehabilitation Engineering and Assistive Technology.

# Contents

# List of Figures

# List of Tables

# Chapter 1

# Introduction

According to the CDC, one third of adults age 65 and older fall every year [1] with between 20% and 30% resulting in a moderate to severe injury [2, 3]. These falls are costly financially and in terms of health and quality of life. Falls among old adults resulted in nearly 2.4 million emergency department visits in 2011, a 46% increase over 2001 with only a 17% increase in the population over age 65 [4]. Over the past 3 decades, the NIH has heavily invested in research of fall prevention programs [5, 6] which have shown only modest effects on fall rates [6, 7, 8, 9, 10].

The causes of falls are often multi-faceted: the result of a combination of age-related changes in physiology and environmental factors. Increased age often brings reductions in sensory acuity [11, 12], muscle strength [13, 14], and cognitive capacity [15], as well as slowed neuromuscular function [13] and diminished executive function [16]; changes that may impair old adults' ability to safely navigate their environments.

In addition to the costs of actual fall-related injuries, fear of falling can also present a serious personal cost to old adults. Individuals who have fallen previously tend to be more fearful of falling, even if their fall did not result in an injury [17, 18]. Fear may then result in its own issues by prompting self-imposed limits on activities or changes in gait. For example, an old adult with a fear of falls may walk with more caution [19] or avoid taking the stairs.

Self-limitation can reduce physical activity, and result in declines in mobility and fitness and lead to a self-fulfilling increase in risk of an actual fall [17, 18, 20]. This highlights the need for interventions that can rehabilitate walking and balance ability in aging adults.

## 1.1 Rehabilitation and Reduction of Falls

The complexity and substantial costs of falls has led the NIH to invest heavily in falls research over the last three decades. Studies funded during this time have resulted in guidelines for falls interventions today. These interventions include regular exercise, medication review, eye exams, and home environment modifications such as adding grab bars and removing tripping hazards [21]. While many of these interventions reduce the risk of falls from external causes, only regular exercise attempts to target physiological causes of falls. Along these lines, a number of falls prevention studies were conducted in the late 1980s and early 1990s as a part of the FICSIT trials [5, 6], focusing on exercise interventions such as strength training, Tai Chi, and aerobic exercise. However, most of these programs have had only modest effects on fall rates [5, 6, 7, 8, 9, 10]. Additionally, in a 2008 study, Kraemer et al. [22] reported that individuals with a history of falls showed no clinically meaningful or statistically significant improvement following four months of physical exercises and rehabilitation. Hence, there is a critical need to develop novel approaches that better address physiological changes associated with aging and truly reduce an individual's innate risk of falling.

One approach to improving gait and balance in old adults that has not been well studied is neuromodulation. Neuromodulation is the use of a device to enhance or suppress neural activity for treatment purposes. The most common neuromodulation device for movement disorder treatment is deep brain stimulation (DBS); however, it requires direct contact with the central nervous system and surgical implantation. Due to the risks, DBS is generally reserved for Parkinson's disease patients who have failed other treatment options [23]. Another option for neuromodulation is transcranial magnetic stimulation (TMS), which is a non-invasive technique. Unfortunately, TMS activates relatively large regions of the cerebral cortex instead of targeting specific pathways. It has not been shown to be effective in rehabilitation of gait or balance [24, 25].

In the early 2000s, researchers at UW-Madison developed a technique called Cranial Nerve Non-Invasive Neuromodulation (CN-NINM) that uses stimulation via the tongue to enhance neuroplasticity during physical rehabilitation exercises. CN-NINM uses a small Portable Neuromodulation Stimulator (PoNS®) (Figure 1.1) device to safely and non-invasively deliver electrical impulses to the brainstem via cranial nerve endings in the tongue. Previous work has shown exceptional promise when 20-minute sessions of stimulation are combined with rehabilitation exercises in subjects with balance impairments secondary to traumatic brain injury [26], multiple sclerosis [27, 28], and vestibular disorders [29, 30].


Figure 1.1: Portable Neuromodulation Stimulator used to deliver Cranial Nerve Non-Invasive Neuromodulation

While the precise neural mechanisms for CN-NINM efficacy remain unidentified, stimulation from the PoNS device may interact with portions of the afferent and efferent pathways in the brainstem and cortex that are involved in locomotor control [31, 32]. For example, an fMRI study showed that balance-impaired subjects exhibited changes in susceptibility to optic flow following one week of rehabilitation with CN-NINM (Fig. 3). Subjects showed decreased activity in the anterior cingulate area (ACC, responsible for resolving conflicts in neural signals from different systems) and increased pons activity in the area of the right trigeminal nucleus (entry point for stimulation into CNS from tongue). The decrease in ACC activity has been postulated to be the result of re-weighted sensory inputs to the balance processing network. Additionally, CN-NINM stimulation has been hypothesized to strengthen connections between the trigeminal and vestibular nuclei leading to increased activity in the trigeminal nuclei due to an increase in flow of information between the nuclei [30]. Enhanced neuroplasticity due to CN-NINM stimulation paired with physical exercises could result in a heightened ability for motor learning during rehabilitation. Prior experience with CN-NINM is summarized in Appendix A.

## 1.2 Gait Evaluation and Fall Risk

Clinical gait evaluation often relies on visual observation and qualitative rating scales, such as the Dynamic Gait Index (DGI; see Appendix C). The DGI is an 8-item inventory of progressively challenging gait tasks (e.g. walk and turn your head, change speeds, navigate stairs) with a maximum score of 24. Studies have shown that scores below 19 indicate a higher risk of falls [33]. Further a 3-point change is considered the minimal detectable change clinically [34].

A growing number of studies suggest that changes in gait performance measures can distinguish old adults with and without a history of falls from young adults. Specifically, gait variability is shown to be a good indicator of dynamic balance; abnormal variability of stride time or step width can predict individuals at a greater risk of falling [35, 36, 37]. A number of specific gait variability metrics have been considered including step duration, step length, and step width [37, 38]. Step width variability may be particularly relevant to falls in old adults since human gait is known to be inherently less stable in the medio-lateral direction [39, 40, 41], and there is ample evidence that injury-inducing falls in old adults most often occur as a result of falls to the side [42]. It is believed that medio-lateral foot placement is a primary strategy to maintain balance in the frontal plane, such that step width variability is indicative of sensorimotor balance control [39, 40, 41].

Previous work has also suggested that old adults with no history of falls may not show differences in gait variability compared to young adults under normal walking conditions. Hence, gait variability during normal walking may not be sufficiently robust to identify old adults at risk of a first fall. In the literature, dual task and challenging single task paradigms have been used to elucidate the influence of age-related changes on walking performance [37, 38, 43, 44, 45, 46, 47]. These challenging walking tasks are often designed to target the functional consequences of aging on sensory, cognitive and/or neuromuscular function. For example, as the integrity of somatosensory and vestibular sensory information begins to degrade past middle age, old adults may become more reliant on visual information, particularly peripheral vision, to maintain balance [48, 11, 12, 49]. Therefore, the use of altered lighting conditions or virtual environments can manipulate sensory feedback and alter gait variability [41, 46, 50]. Additionally, there is evidence that cognitive capacity and executive function may be reduced in old age [15, 16]. Attention-demanding tasks during walking, such as mathematical calculations, have also been shown to preferentially increase gait variability in old adults [43, 44, 45]. Finally, as neuromuscular function slows with age, old adults may have more difficulty with tasks that manipulate foot placement using balance beams or obstacles, reflecting an inability to cope with challenges present in the physical environmental [47]. These additional task requirements have shown promise to expose age-related differences in balance during walking; however, their relative effects in a normal aging population are not yet well understood.

In addition to gait variability metrics, electromyographic (EMG) recordings of leg muscles have shown that old adults use different muscle recruitment strategies than young adults [51]. Old adults often walk with a greater amount of antagonist leg muscle co-activation than younger adults, which may be a strategy to increase leg joint stiffness and increase stability during walking [52].

## 1.3 Dissertation Overview

My dissertation research focuses on two broad aspects of walking and balance in old adults. First, I assess the efficacy of various gait challenges to distinguish the effects of aging. Second, I also investigate whether CN-NINM can enhance balance in old adults with idiopathic fall risk. My overall premise is that aging compromises the integration and neural processing of sensory information that underlies human balance control and that CN-NINM training may improve old adults' ability to process sensory information to effectively maintain balance. While electrical stimulation via the tongue has been explored in previous studies as a potential treatment for various neurological etiologies (vestibular loss [29, 53], multiple sclerosis [27, 28], and traumatic brain injury [26]), it has not been specifically studied as a means of fall prevention in old adults with no concurrent neurological diagnosis. In line with these foci, this research has three aims.

### Aim 1

**Investigate the relative influence of visual perturbation, cognitive load and physical challenges on gait variability metrics across age and falls history status.**

Age-related physiological changes may include reduced sensory acuity, diminished executive function, reduced cognitive capacity, decreased muscle strength, and slowed neuromuscular function. While a given individual may not be clinically deficient in any one of these areas, a combination of subtle deficits could compromise their ability to maintain balance in certain circumstances. Gait variability, particularly variability of step width, has been used to characterize balance control during gait. However, studies have frequently found that during normal walking, old adults with no history of falls show no substantial difference in step variability compared to young adults. In order to differentiate between groups, a more difficult or secondary task that challenges the physiological deficits of one group is often needed. It has been well established that old adults at risk for falls exhibit balance difficulties when provided conflicting visual information [54], when challenged with a secondary cognitive task that divides attention [43], and when presented with a challenging physical task [55]. Presuming that gait variability characterizes dynamic balance and fall risk, a scenario that causes a substantial, involuntary increase in variability could reveal conditions that may lead to a loss of balance. To complete this aim, I recruited 12 young adults (age: 23.6 ± 3.9 years), 14 healthy old adults (70.5 ± 4.5 years), and 2 old adults with an increased risk of falls (age: 72.0 ± 5.7 years). In total, six of the old adults had reported falling in the past year. These subjects participated in treadmill gait tests with four conditions: normal walking, visual perturbations (Figure 1.2b), a cognitive dual task, and narrow step width. The mean and variability of spatiotemporal gait parameters were characterized for each subject and averaged across groups (Figure 1.2c). I hypothesized that increasing the difficulty of a walking task by changing the task requirements or adding a secondary task would increase step width variability in all subjects, but the magnitude of the increase would be greater in old adults than in young and greater still in old adults with a history of falls compared to those without such a history.

## Aim 2

**Investigate the effects of age on muscular coordination of walking in the presence of altered visual input and attention-dividing dual-tasks.**

The premise of CN-NINM training is that the brain stimulation enhances neuroplasticity and learning, resulting in improved integration and neural processing of the sensory information that underlies human balance control. Antagonist muscle co-activation is heightened in old adults, and thought to arise in part from impaired sensorimotor performance, and is typically considered an indicator of an individual feeling at risk of falling [48, 52]. To complete this aim, subjects from Aim 1 underwent quantitative electromyography (EMG). I assessed muscle coordination as subjects walked under the normal, visual, and cognitive dual-task conditions in Aim 1. Muscle activation patterns were used to characterize antago-

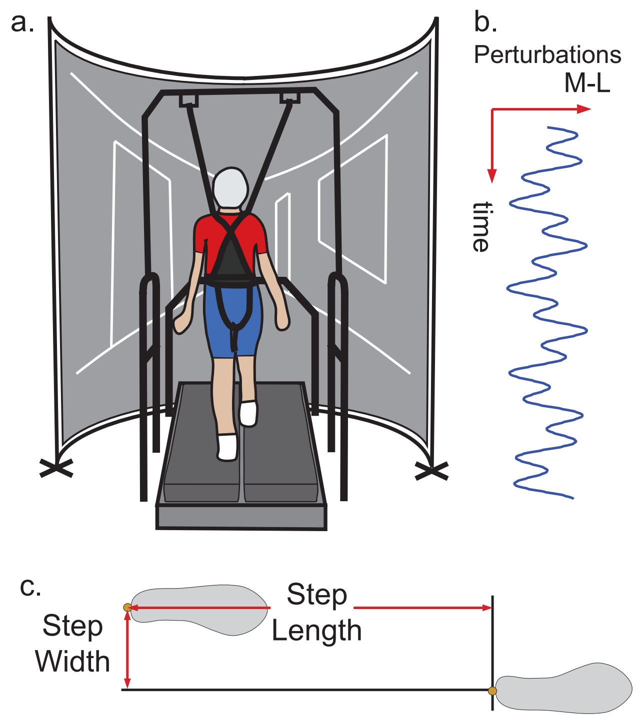



Figure 1.2: Experimental setup. 1a. Subject walks on a split-belt treadmill surrounded by a semi-circular projection screen. A rear-projected virtual hallway moved at the same speed as the treadmill. Old adults wore a harness during testing that was adjusted to prevent falls but still allow free movement around the treadmill surface. 1b. During the visual perturbation trial, we added a mediolateral perturbation consisting of a sum of sinusoids to the virtual hallway motion. 1c. Step width and step length were calculated from heel kinematic data for both left-right and right-left steps.

nist muscle co-activation. For this aim, I hypothesized that old adults would have increased co-activation during normal walking compared to young adults and that this difference would increase when gait was challenged.

## Aim 3

**Investigate the effect of CN-NINM enhanced training on gait variability, postural balance, and clinical metrics of fall risk in old adults.**

Gait variability, postural balance, and clinical metrics of gait and balance can delineate old adults with a history of falls. Improvement on scores in these areas may indicate a lowered risk of falls. For example, reducing the influence of the gait challenges in Aim 1 on step width variability could denote a reduced sensitivity to disturbances of balance while walking. Likewise, lower scores on two clinical tests (the dynamic gait index (DGI) and the sensory organization test (SOT)) have been tied to increased fall risk [56]. Previous studies using CN-NINM as an intervention in other populations have shown significant improvements in DGI and SOT scores [26, 27, 30], with some subjects approaching the maximum DGI score. To complete this aim, the old adults from Aim 1 were invited to participate in 2 weeks of supervised gait and balance exercises with pre- and post-training evaluations of the gait variability measures in Aim 1, postural balance, and clinical metrics of falls risk (DGI and SOT). Subjects were randomized to use active or placebo CN-NINM stimulation during the exercises. I hypothesized that subjects receiving active CN-NINM stimulation would show greater improvement in step width variability, postural balance, and clinical metrics of fall risk than subjects receiving the same training with placebo stimulation.

## Overview of Chapters

In the chapters and appendices that follow, I explore the three aims. Chapter 2 focuses on Aim 1 and compares gait variability in healthy young and old adults when walking with a visual perturbation, cognitive challenge, and narrowed step width. I found that the visual perturbation used in this study was the only one that made a significant impact on gait variability in old adults and had no significant effects in young adults. Chapter 3 investigates Aim 2 by exploring the effects of visual perturbation and a cognitive dual task on muscle activity and co-activation patterns in young and old adults. I found that old adults had increased muscle activation compared to young adults at various points of the gait cycle in both normal and challenged walking conditions. The results in co-activation depended substantially on the definition used, but the visual condition was the most likely to increase co-activation in old adults compared to both normal walking and young adults. Chapter 4 focuses on the outcomes of Aim 3. In general, I did not find significant effects of active CN-NINM stimulation compared to sham CN-NINM. Chapter 5 summarizes the overall study, some possible reasons for the outcome, and suggests future directions for this and related work. Prior work using CN-NINM, including early pilot work with Traumatic Brain Injury patients and a study with healthy young adults is described in Appendix A. Appendix B summarizes additional data collected to analyze the effects of CN-NINM training in this population, namely a pre-post analysis of EMG data.

# Chapter 2

# Gait variability in healthy old adults is more affected by a visual perturbation than by a cognitive or narrow step placement demand

Note: This chapter has been published previously in Gait & Posture. The original version can be found at DOI: http://dx.doi.org/10.1016/j.gaitpost.2015.07.006.

## 2.1 Abstract

*Gait variability measures have been linked to fall risk in older adults. However, challenging walking tasks may be required to elucidate increases in variability that arise from subtle age-related changes in cognitive processing and sensorimotor function. Hence, the study objective was to investigate the effects of visual perturbations, increased cognitive load, and narrowed step width on gait variability in healthy old and young adults. Eleven old (OA, 71.2 ± 4.2 years) and twelve young (YA, 23.6 ± 3.9 years) adults walked on a treadmill while watch-*

*ing a speed-matched virtual hallway. Subjects walked: 1) normally, 2) with mediolateral visual perturbations, 3) while performing a cognitive task (serial seven subtractions), and 4) with narrowed step width. We computed the mean and variability of step width (SW and SWV, respectively) and length (SL, SLV) over one three minute trial per condition. Walking normally, old and young adults exhibited similar SWV and SLV. Visual perturbations significantly increased gait variability in old adults (by more than 100% in both SWV and SLV), but not young adults. The cognitive task and walking with narrowed step width did not show any effect on SWV or SLV in either group. The dramatic increase in step width variability when old adults were subjected to mediolateral visual perturbations was likely due to increased reliance on visual feedback for assessing whole body position. Further work is needed to ascertain whether these findings may reflect sub-clinical balance deficits that could contribute to the increased fall risk seen with advancing age.*

## 2.2 Introduction

Approximately one-third of adults over 65 fall annually with a majority of these falls occurring during locomotion [1]. The underlying causes of these falls presumably arise from a number of physiological factors including reduced sensory acuity [11, 12], diminished executive function [16], reduced cognitive capacity [15], decreased muscle strength [13, 14], and slowed neuromuscular function [13]. Although these phenomena are common features of aging, the manner in which they affect balance function during walking is not well understood. For example, even if an individual scores in the normal range for all of these physiological areas, subtle age-related changes may disrupt old adults' ability to maintain balance in a challenging environment and contribute to a first fall.

Prior studies have used gait variability to characterize balance during walking [41, 38, 44]. In fact, substantial differences in gait variability (e.g. standard deviation or coefficient of variation of stride time, step width or step length over many steps) have been reported between old adults with and without a history of falls [37, 35]. Compromised mediolateral balance is particularly relevant as it requires fine sensorimotor control of foot placement from step to step [41]. However, healthy old adults often exhibit gait variability similar to young adults during normal, unencumbered walking [16]. Hence, gait variability during normal walking may not be sufficiently robust to identify old adults at risk of a first fall.

In the literature, challenging walking task paradigms have been used to elucidate the influence of age-related changes on walking performance [38, 44, 37, 45, 46, 43, 47]. These challenging walking tasks are often designed to target the functional consequences of aging on sensory, cognitive and/or neuromuscular function. For example, the use of altered lighting conditions, vibrating insoles or virtual environments can manipulate sensory feedback and alter gait variability [41, 46, 50]. Attention-demanding tasks during walking, such as mathematical calculations, have also been shown to preferentially increase gait variability in old adults [44, 43]. Finally, manipulating foot placement using balance beams or obstacles may reveal differences in neuromuscular function, reflecting an inability to cope with challenges present in the physical environment [47, 40]. These additional task requirements have shown promise to expose age-related differences in balance during walking; however, their comparative effects are not yet well understood.

The purpose of this study was to investigate the effects of perturbed visual feedback, increased cognitive load, and narrowed step width demands on gait variability in healthy old and young adults. We first hypothesized that during unencumbered walking, old and young adults would walk with similar step width variability (SWV) and step length variability (SLV). Second, with the addition of challenging task requirements, SWV and SLV would increase more in old adults than young adults. Our clinical motivation was to identify relative increases in old adults' SWV and SLV that point to opportunities for early diagnosis of age-related balance deficits.

## 2.3 Methods

### Subjects and Experimental Protocol

Eleven old adults (mean ± standard deviation; age: 71.2 ± 4.2 years, height: 1.64 ± 0.06 m, mass: 66.9 ± 9.6 kg, 10 female) and twelve young adults (age: 23.6 ± 3.9 years, height: 1.69 ± 0.25 m, mass: 70.7 ± 11.3 kg, 7 female) participated in this study. Subjects were included if they walked without an assistive device, were free of orthopedic injuries in the prior six months, had no neurological injury or pathology, and met the American College of Sports Medicine cardiovascular guidelines for exercise. Additionally, subjects could not have experienced an unexpected fall [57] in the previous six months. They were also required to score in the normal range on the Dynamic Gait Index (DGI) [58], a series of eight walking tasks (eg. turning one's head while walking, changing speeds, navigating stairs) each worth up to three points. Individuals scoring below 19 are considered to be at an increased risk of falling. The old adults in this study scored an average of 23.8 ± 0.6 on the DGI. All subjects provided written informed consent as per the University of Wisconsin-Madison Health Science Institutional Review Board.

At the beginning of each session, subjects walked along a 10 m walkway at a comfortable pace. We used the average of two times taken to traverse the middle 6 m of the walkway to prescribe subjects' treadmill speed. During the treadmill familiarization period, three old adults reported being unsure that they could complete the treadmill walking trials at their over-ground speed. We therefore reduced the treadmill speed by 10% for these subjects. To ensure subject safety, old adults used a harness during treadmill testing that was adjusted such that it would prevent a full fall, but was slack enough to allow free movement around the treadmill surface without providing substantial haptic feedback. Subjects then completed a series of four 3-minute walking trials on a split-belt instrumented treadmill (Bertec, Columbus, OH) presented in a random order. The four conditions included normal walking (Normal), mediolateral visual perturbations (Visual), a cognitive challenge (Cognitive), and

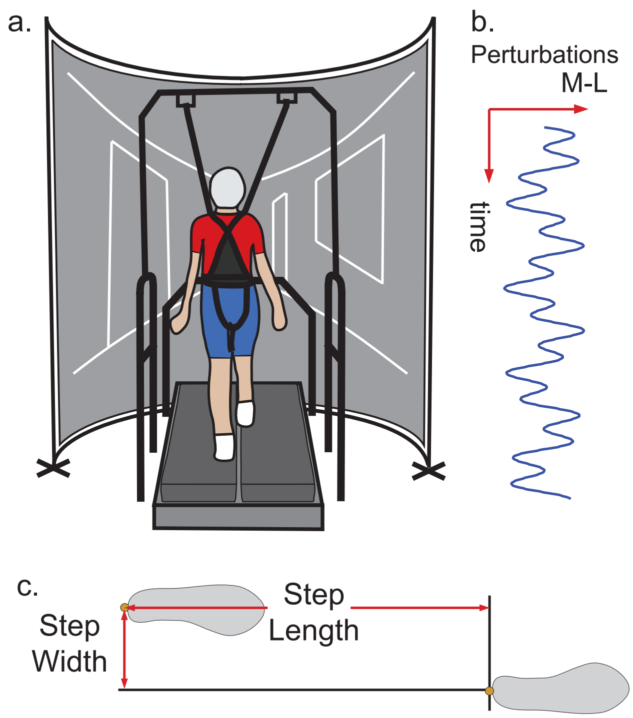



Figure 2.1: Experimental setup. 1a. Subject walks on a split-belt treadmill surrounded by a semi-circular projection screen. A rear-projected virtual hallway moved at the same speed as the treadmill. Old adults wore a harness during testing that was adjusted to prevent falls but still allow free movement around the treadmill surface. 1b. During the visual perturbation trial, we added a mediolateral perturbation consisting of a sum of sinusoids to the virtual hallway motion. 1c. Step width and step length were calculated from heel kinematic data for both left-right and right-left steps.

narrow step width (Narrow), each described in detail below. All tasks were performed with the subject facing a semi-circular rear-projection screen, which displayed a virtual hallway moving at the same speed as the treadmill (Figure 2.1 a). This system was described in more detail by O'Connor, et al. [41]. To investigate the confounding effects of walking speed, young adults repeated all conditions at 80% of their preferred speed.

For the normal walking condition, subjects were asked to walk normally while watching the virtual hallway. During the visual perturbation condition, a continuous mediolateral motion consisting of the sum of two sinusoids (0.135 and 0.442 Hz) with 0.175 m amplitudes was added to the speed-matched virtual hallway (Figure 2.1 b) [41, 50]. This mediolateral motion was applied such that the fore-ground translated at the full amplitude of the perturbation while the end of the hall remained nearly stationary. This ensured that perturbations challenged walking balance and not control of heading. During the cognitive challenge condition, subjects walked while counting backwards by sevens starting at a prescribed random three-digit number [16]. In the event that subjects reached zero before the trial was complete, they continued from a new prescribed three-digit number. For the narrow step width task [47], subjects were asked to place each step on the 1 cm gap separating the two treadmill belts as if they were on a balance beam. During this trial, subjects were allowed to look at their feet as needed.

## Measurements and Data Analysis

Three dimensional pelvic and foot kinematics were recorded at 100 Hz using a passive motion capture system (Motion Analysis, CA) to track retro-reflective markers placed on the sacrum and both heels. Kinematic data were low-pass filtered at 8 Hz using a 4th order Butterworth filter. We then identified heel strikes from peaks in the fore-aft position of the heel markers relative to the sacral marker [59]. We computed right-left and left-right step width (SW) values from consecutive mediolateral heel positions averaged over a period from 12-25% of the gait cycle (heel-strike to heel-strike), corresponding to mid-stance prior to heel-rise [60], (Figure 2.1 c). Step length (SL) was computed as the relative fore-aft position of successive heel markers at 20% of each gait cycle plus the treadmill translation over the duration of that step [50]. We characterized gait variability as the standard deviation of step width and step length over all steps performed within a 3-minute trial (old: $345 \pm 31$ steps, young: $332 \pm 17$ steps). All mean and variability metrics were normalized to subject leg length (%LL).

## Statistical Analysis

We first confirmed normal distribution using a Kolmogorov-Smirnov test (STATISTICA, StatSoft, Tulsa, OK). We used a repeated measures ANOVA with a Tukey Honest Significant Differences (HSD) post-hoc test to test for significant effects of age (old vs. young) and condition (Normal, Cognitive, Visual, Narrow) on mean step width, mean step length, SWV and SLV using an $\alpha < 0.05$ criterion. Corrections for heterogeneous variances, determined from Levene's Test, were used when necessary. Within groups, we focused on comparisons between normal and challenging task conditions. Between groups, we focused on comparisons between young and old adults under the same task conditions. We used t-tests to investigate significant effects of speed (80%, 100% preferred) on step width and length metrics in young adults for each condition (Normal, Cognitive, Visual, Narrow).

## 2.4 Results

There were no significant differences in normalized preferred walking speed on the treadmill between old (1.24 m/s or 1.68 $\pm$ 0.12 LL/s) and young (1.36 m/s or 1.68 $\pm$ 0.19 LL/s) adults (leg-length normalized, T-Test, $F1, 21 = 2.44$,$p = 0.928$). Group values for SW, SL, SWV, and SLV are summarized in Table 2.1 along with the ANOVA results.

### Average Step Width and Step Length

Compared to walking normally, old adults walked with 5% shorter steps during the visual perturbation condition (Tukey, $p < 0.001$) (Figure 2.2). Additionally, and by design, both young and old adults walked with significantly narrower steps during the narrow SW condition compared to normal walking (OA: 66% reduction on average, YA: 93% reduction, Tukey, $p$'$s < 0.001$).

### Variability of Step Width and Step Length

Old and young adults exhibited similar step width variability (SWV, OA vs. YA, 3.5 $\pm$ 1.4 %LL vs. 2.9 $\pm$ 0.5 %LL, Tukey, $p = 0.996$) and step length variability (SLV, 2.9 $\pm$ 0.6 %LL vs. 2.6 $\pm$ 0.7 %LL, Tukey, $p = 0.998$) during normal walking (Figure 2.3, Figure 2.2). During the visual perturbation condition, young adults did not exhibit a significant change

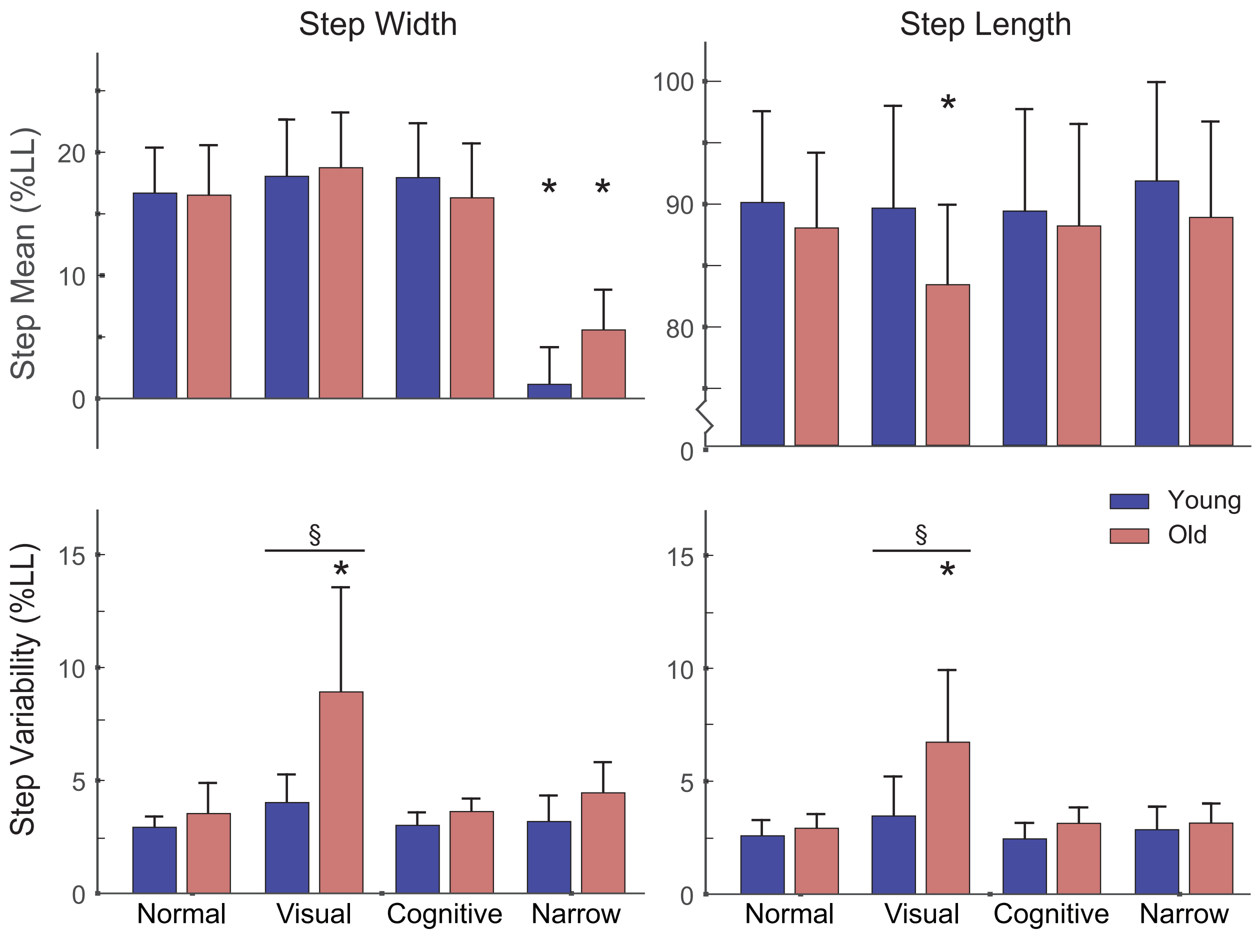



Figure 2.2: Summary step placement results for all subjects. Group mean ± standard deviation are represented. An asterisk (*) denotes a significant within-group difference between a challenging condition and normal walking ($p < 0.01$). A section sign (§) and horizontal line denote a significant between-group difference ($p < 0.01$) within a condition.

SWV (Tukey, $p = 0.898$) or SLV (Tukey, $p = 0.718$) relative to normal walking. However, old adults exhibited greater SWV and SLV than young adults (Tukey, $p$'$s < 0.001$) in the visual perturbation condition, with both variability metrics increasing significantly relative to the normal walking condition (+152% and +131% increase in mean SWV and SLV, respectively, Tukey, $p$'$s < 0.001$). Compared to walking normally, neither group exhibited significant changes in SWV or SLV during the cognitive task (Tukey; $p$'$s \geq 0.999$) or the narrow step width condition (Tukey; $p$'$s \geq 0.888$).

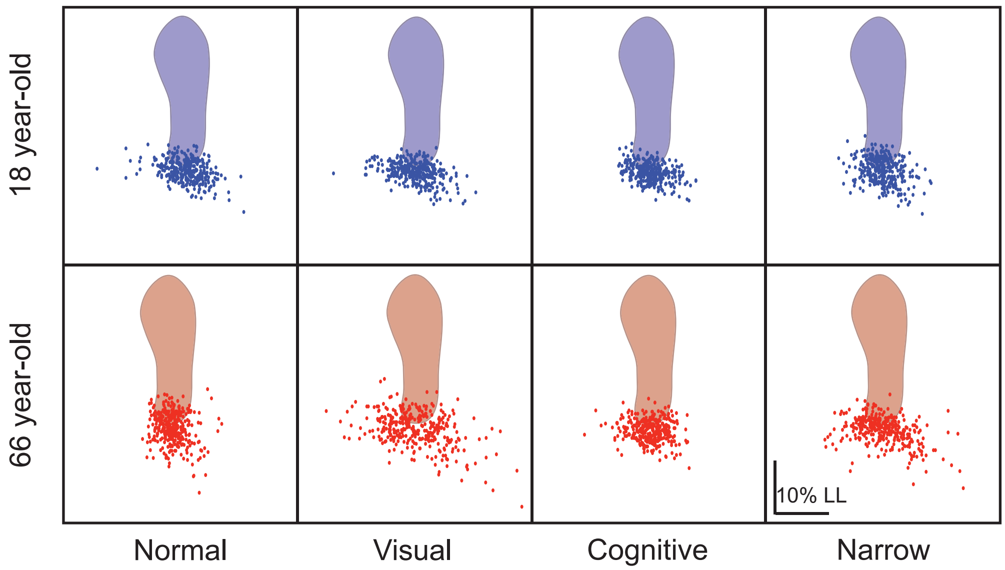



Figure 2.3: For representative subjects, the distribution of step width and step length values about the mean are plotted for each walking trial. Each small dot represents the step width and step length for a single step, measured from heel markers. Scatter along the horizontal and vertical axes represents variability in SW and SL, respectively. The scatter of SW and SL values is fairly tight for both subjects in all but the visual perturbation trial. Note the wide range of step placements for the old adult in the visual condition.

Table 2.1: Group mean (± standard deviation) values for SW, SL, SWV, and SLV during each condition are listed for old and young adults walking at preferred speed. Group and condition main effects or interactions from a repeated measures ANOVA are reported.

| Metric | Group | Normal | Visual | Cognitive | Narrow | Effect | *DoF* | *F* | *p* |
|---|---|---|---|---|---|---|---|---|---|
| SW | Old | 16.52 (1.17) | 18.75 (1.37) | 16.3 (1.46) | 5.57 (0.95) | Group | 1,21 | - | 0.569 |
| | Young | 16.68 (1.12) | 18.05 (1.32) | 17.94 (1.40) | 1.14 (0.91) | Condition | 3,63 | 155.35 | **<0.001** |
| | | | | | | Group × Condition | 3,63 | 5.21 | **0.003** |
| SL | Old | 88.06 (2.06) | 83.44 (2.27) | 88.22 (2.16) | 88.92 (2.39) | Group | 1,21 | - | 0.304 |
| | Young | 90.13 (1.98) | 89.67 (2.17) | 89.43 (2.07) | 91.89 (2.29) | Condition | 3, 63 | 10.88 | **<0.001** |
| | | | | | | Group × Condition | 3, 63 | 5.13 | **0.003** |
| SWV | Old | 3.53 (0.30) | 8.92 (1.00) | 3.62 (0.28) | 4.45 (0.38) | Group | 1, 21 | 12.05 | **0.002** |
| | Young | 2.93 (0.29) | 4.02 (0.96) | 3.01 (0.27) | 3.18 (0.36) | Condition | 3, 63 | 20.20 | **<0.001** |
| | | | | | | Group × Condition | 3, 63 | 9.14 | **<0.001** |
| SLV | Old | 2.92 (0.20) | 6.73 (0.77) | 3.13 (0.22) | 3.15 (0.29) | Group | 1, 21 | 8.79 | **0.007** |
| | Young | 2.58 (0.19) | 3.46 (0.73) | 2.45 (0.21) | 2.85 (0.28) | Condition | 3, 63 | 17.85 | **<0.001** |
| | | | | | | Group × Condition | 3, 63 | 7.12 | **<0.001** |

## Effect of Walking Speed

When young adults walked at 80% preferred speed (1.08 ± 0.09 m/s or 1.35 ± 0.19 LL/s), SW and SLV were very similar for each condition to walking at preferred speed (T-test, $p$'$s \geq 0.372$). SWV was also not significantly different between speeds (T-test, $p$'$s \geq 0.107$)

(Figure 2.4). Only step length was significantly affected when young adults walked more slowly (-14% decrease in average SL; T-test, $p$'s $< 0.001$).

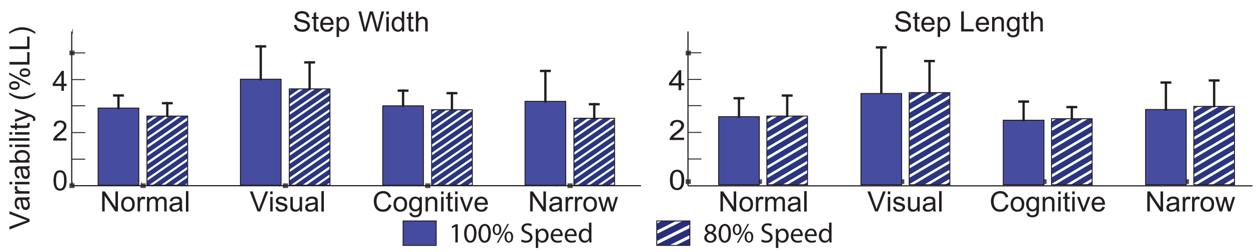



Figure 2.4: Young adults performed all trials at 100% and 80% of their preferred overground walking speed. Walking slower elicited shorter steps ($p$'s $< 0.001$) for each condition, but there were no differences in step width variability or step length variability.

## 2.5 Discussion

Gait variability has emerged over the last two decades as a promising metric for characterizing dynamic balance [41, 38, 44] and altered variability has been linked to old adults with a history of falls [16, 37, 35]. At the same time, the need for challenging tasks to distinguish between old and young adults has also been highlighted [38, 44, 37, 45, 46, 43, 47]. As hypothesized in this study, SWV and SLV were statistically indistinguishable between healthy young and healthy old adults with no falls history during normal, unencumbered walking. Further, in partial support of our second hypothesis, walking with mediolateral visual perturbations induced changes in SWV and SLV that were able to distinguish old and young adults. This observation suggests that aging may bring a greater reliance on visual feedback to maintain balance during walking, an observation that is consistent with postural control studies [48, 61, 62] and has broad relevance for both balance assessment and the design of falls prevention programs. Surprisingly, and in contrast with our second hypothesis, we did not see any difference in SWV or SLV between old and young adults in response to either an increased cognitive load or narrow step placement demands.

Why do old adults seemingly exhibit such heightened sensitivity to aberrant visual feedback during gait? To understand this, it is first imperative to recognize the importance of lateral step placement to the maintenance of balance in walking. Biomechanical models of gait have shown that frontal plane balance is inherently unstable, but easily stabilized by choosing where to step relative to the body center of mass kinematics [41, 63]. To accomplish this, multi-modal sensory feedback is needed to assess the whole body kinematic state, with sensory integration and sensorimotor processing then critical to executing step placement. Thus, it seems that old adults place a greater reliance, or increased gain, on visual feedback to assess the body's kinematic state, perhaps compensating for age-related decrements in vestibular function [12] and somatosensory feedback from the periphery [11, 49]. There is also evidence that old adults may be particularly reliant on peripheral vision [48], which was stimulated to a large degree by the visual perturbations used in this experiment. Alternatively, old adults may be less capable of down-weighting aberrant visual information [61, 62]. In either scenario, old adults would incorrectly assess their kinematic state based on the flawed visual information leading to an inappropriate step placement relative to the center of mass. Incorrect step placement can then further compromise mediolateral balance, requiring subsequent recovery steps to restore balance, thereby contributing to the increase in step width variability observed here. Interestingly, we previously found that the visual perturbation frequencies permeate old adult's center of mass motion [64]. That old adults' gait patterns entrain to one or both of the frequencies used in the perturbed visual flow further supports the idea that they were relying upon the aberrant visual feedback in their sensorimotor control of walking.

Contrary to prior studies, the cognitive task in this study did not induce changes in SWV or SLV in old adults [38, 44, 45, 43]. Our study is therefore in line with the study by Springer, et al. which found that a cognitive task affected gait variability in old adults with a history of falls, but did not affect old adults with no history of falls [16]. That study also found that impaired executive function was strongly associated with increased swing time variability in old adults with a history of falls. One interpretation of these findings is that cognitive challenges interfere with central regulation of periodic movement patterns. The old adults in this study may not have been affected by the cognitive task because the specific activity (serial 7 subtractions) was not sufficiently challenging to disrupt this regulation in the healthy old population tested in this study.

During the narrow step width condition both groups were able to effectively narrow their step width when asked. On average, old adults had a wider step width during this task but the difference between groups was not significant ($p = 0.204$). We also did not find significant effects of this task on SWV or SLV. These conclusions are in contrast with prior studies [47], though our variability measures are comparable to the values reported by Dean et al. [40].

Slower absolute walking speeds are often seen with increasing age and have been tied to a variety of health issues, including fall risk [65]. However, deleterious effects are most frequently found in individuals with a preferred walking speed below 1.0 m/s, nearly 20% slower than the old adults in this study [66]. Additionally, the old adults in this study did not show any significant differences in normalized walking speed from young adults. Thus, gait speed would seem insufficient to explain the differences in gait variability we observed between groups. Further, when young adults were asked to voluntarily reduce their walking speed, we observed no significant changes in their gait variability metrics. Thus, the age-related effects we observed most likely reflect robust age-related differences in the control of balance.

There are some limitations of this study that are relevant to consider in interpreting our findings. First, we only considered one specific visual perturbation consisting of a mediolateral rotation of the visual field. Other studies have shown that young adult gait variability depends on visual perturbation direction, magnitude, and frequency content [41, 50], such that further study is needed to determine the visual conditions to which old adults may be most sensitive. Second, the reliability of gait variability has been questioned by some in the gait community [67], with others suggesting that the precision and robustness of gait variability can be improved by using longer trials to allow the inclusion of larger numbers of steps [68, 69, 70]. Accordingly, our experiments were performed on a treadmill which permitted the collection of 300+ steps/trial to characterize gait variability. However, while the use of a treadmill allowed us to collect large numbers of steps, treadmill walking regularizes walking speed and may induce gait variability values that differ from those seen overground [35, 71]. Finally, to ensure their safety, the old adults in the study used a harness while walking on the treadmill. While the harness was adjusted to ensure that subjects' movement was not restricted, it is still possible that tactile feedback from the harness could have influenced our results.

Further work is needed to determine whether the visual perturbation technique used in this study could be used to identify subtle sensory deficits that could eventually lead to falls in old adults. Adding clinical metrics of sensory acuity to future studies would allow us to investigate whether the increase in gait variability induced by visual perturbations may arise from deficits in, for example, peripheral sensation. Further, it will be important to extend the data set to include old adults with clinical balance deficits and/or a history of falls. These future studies could lead to the development of a low-cost battery of tests to enable early detection of balance deficits and targeted falls prevention programs in old adults.

In summary, we have shown that perturbed visual feedback was sufficient to induce greater gait variability in healthy old adults relative to young adults, but that increased cognitive load and narrow step width demands were ineffective in delineating the two groups. The dramatic increase in step width variability when old adults were subjected to mediolateral visual perturbations was likely due to increased reliance on visual feedback for assessing whole body position. Further work is needed to ascertain whether these findings may reflect sub-clinical balance deficits that could contribute to the increased fall risk seen with advancing age.

# Chapter 3

# Effects of Age on Muscle Coordination in Walking in the Presence of Optical Flow Perturbations and Attention-Dividing Tasks

## 3.1 Abstract

*Muscle co-activation has shown to be greater in old adults compared to young during normal walking and has been linked to fear of falling. Prior work has also linked attention-dividing tasks and inaccurate visual feedback to increases in fall risk in old adults. The objective of this study was to investigate the response of muscle control patterns in healthy young and old adults to a similar set of tasks. Sixteen old (OA, 10.7 ± 4.5 years) and twelve young (23.6 ± 3.9 years) walked on an instrumented treadmill while watching a speed-matched virtual hallway. They completed a three-minute trial with each of three conditions: normal walking,*

*walking with incorrect visual information, and walking with a dual-task cognitive challenge (serial seven subtractions). We recorded electromyography (EMG) bilaterally from the medial hamstring (MH), vastus lateralis (VL), medial gastrocnemius (MG), soleus (SL), and tibialis anterior (TA). Muscle activation during five phases of the gait cycle was computed and compared between walking conditions and age groups. Further, we computed muscle co-activation for MH-VL, MG-TA, and SL-TA pairs using three techniques: the non-normalized overlap in activation, Winter's formula, and Rudolph's formula. Only the SL-TA pair exhibited a difference in young-old co-activation during normal walking, and then only using Rudolph's formula. Muscle activations were not substantially altered in the attention-dividing task. However, the inaccurate visual feedback condition significantly increased muscle co-activation in the old adults, both in comparison to normal walking and relative to young adults. It was concluded that aging is associated with an increased reliance on visual information to maintain balance during walking, with aberrant visual fields causing old adults to adapt their coordination to accommodate the perceived threat to balance.*

## 3.2 Introduction

Age-related changes in gait are associated with a higher risk of falls in old adults with approximately one in three falling annually [1]. Underlying this increased risk may be declines in the quality and integration of sensory feedback [11, 12], cognitive processing [16, 15], strength and speed of muscle activation [13, 14] and muscle coordination [13]. Old adults may compensate for sensorimotor deficits by increasing their use of muscle co-activation to stiffen their joints in an attempt to enhance stability [51]. Prior studies have suggested that the reliance on co-activation muscle co-activation may be more pronounced as a protective mechanism adopted in situations where balance is challenged [18]. Further, several studies have shown greater muscle co-activation in older adults with a fear of falling when compared to those with no fear [72, 73].

In addition to muscle co-activation, variability of spatiotemporal gait parameters to quantify changes in gait due to aging or disease state has gained popularity in recent years. Studies have shown that old adults' balance may be particularly vulnerable in situations where physiological systems in decline are challenged, responding differently or adopting more protective mechanisms than young adults. For instance, dual task conditions that divide attention have been shown to compromise balance in healthy old adults [44, 45]. One of the most common dual task conditions is serial seven subtraction, in which subjects are asked to start at a given number and count backwards in increments of seven. In contrast to this, we have recently shown that gait variability of healthy old adults is not significantly altered by an attention-dividing task. However, medio-lateral perturbation of the visual field has a significant and profound effect on step width and length variability when compared to young adults [74, 64]. These data suggest that old adults are placing a premium on visual feedback to modulate step width and maintain balance during walking.

The purpose of this study was to investigate relative effects of dual task conditions and incongruent visual information on the utilization of muscle activation and co-activation patterns during walking in old and young adults. We hypothesized that muscle co-activation would be higher for old adults compared to young adults during normal walking, and that co-activation would increase more in old adults than young adults when provided with inaccurate visual information.

## 3.3 Methods

This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board (IRB). All subjects provided informed consent before participating in the study. Twelve young (age: 23.6 $\pm$ 3.9 years, height:1.69 $\pm$ 0.25m, mass: 70.7 $\pm$ 11.3 kg, 7 female) and sixteen old adults (70.7 $\pm$ 4.5 years, 1.65 $\pm$ 0.05 m, 69.7 $\pm$ 11.1 kg, 15 female) were asked to walk on a treadmill for three minutes with each of three conditions: normal

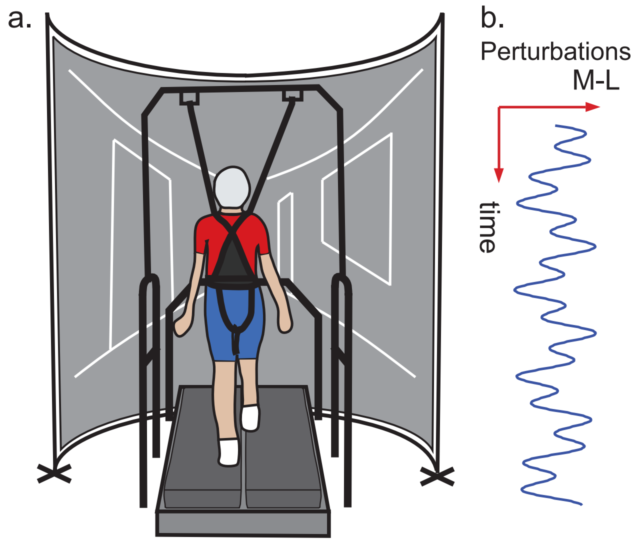



Figure 3.1: Experimental setup. 1a. Subject walks on a split-belt treadmill surrounded by a semi-circular projection screen. A rear-projected virtual hallway moved at the same speed as the treadmill. Old adults wore a harness during testing that was adjusted to prevent falls but still allow free movement around the treadmill surface. 1b. During the visual perturbation trial, we added a mediolateral perturbation consisting of a sum of sinusoids to the virtual hallway motion.

walking, walking with incongruent visual information, and dual-task walking.

Subjects walked in a virtual hallway back-projected on a semi-circular screen surrounding the front of the treadmill (Figure 3.1). For the normal and dual-task conditions, the hallway moved at the same speed as the treadmill. During the trial with incongruent visual information, a pseudo-random mediolateral translation was applied on top of the normal motion of the hallway. This perturbation was the sum of two sine waves at 0.135 and 0.442 Hz with amplitude of .175m. Further the perturbation was applied such that the end of the hallway moved very little relative to the foreground.

Motion capture and electromyography (EMG) data were collected synchronously. EMG was collected bilaterally from the semitendinosus (MH), vastus lateralis (VL), medial gastrocnemius (MG), soleus (SL), and tibialis anterior (TA) muscles. Kinematic data was used to delineate gait cycles.

EMG data was band-pass (1-350 Hz) filtered to remove noise and drift, then rectified and low-pass filtered at 10 Hz to obtain the muscle activation envelope (Figure 3.2). The

RMS average of the normal trial was computed to obtain a normalization factor for each subject. Using the kinematic data, EMG data was split into gait cycles and interpolated to 1000 points per gait cycle then ensemble averaged (300+ steps/trial) for each subject and normalized to the RMS value computed earlier. The muscle activation traces were compared across groups and conditions at five intervals [51]: loading response (0-10%), mid-stance(10-30%), terminal stance/pre-swing (30-60%), initial swing (60-73%), and terminal swing (87-100%). We computed co-activation indices three ways – as the area of overlap between two muscles, as the normalized area of overlap per Winter's definition [75] (Figure 3.2) and as the integral of the ratio of activation ($\leq$1) of the two muscles multiplied by their sum according to Rudolph's formulation [76], for muscle pairs Medial Hamstring-Vastus Lateralis (MH-VL), Medial Gastrocnemius-Tibialis Anterior (MG-TA), and Soleus-Tibialis Anterior (SL-TA) (Figure 3.3.

## 3.4 Results

Overall effects of various conditions and age on EMG patterns and co-activation are summarized in Tables 3.1 and 3.2. In general, the visual trial had the biggest effect of any condition and the old adults were most affected.

### Young Condition Effects

Compared to normal walking, young adults showed no change in muscle activation during most phases of the gait cycle in response to the visual perturbation trial (Figure 3.4). If the correction for a positive Levene's test in the normal trial is taken into account, young adults had an increase in TA activity during terminal swing in the dual-task trial versus normal, the difference is not significant if this correction is not made. Young adults also had a tendency to have increased TA activation in the dual-task trial during initial swing compared to normal ($p = 0.065$).

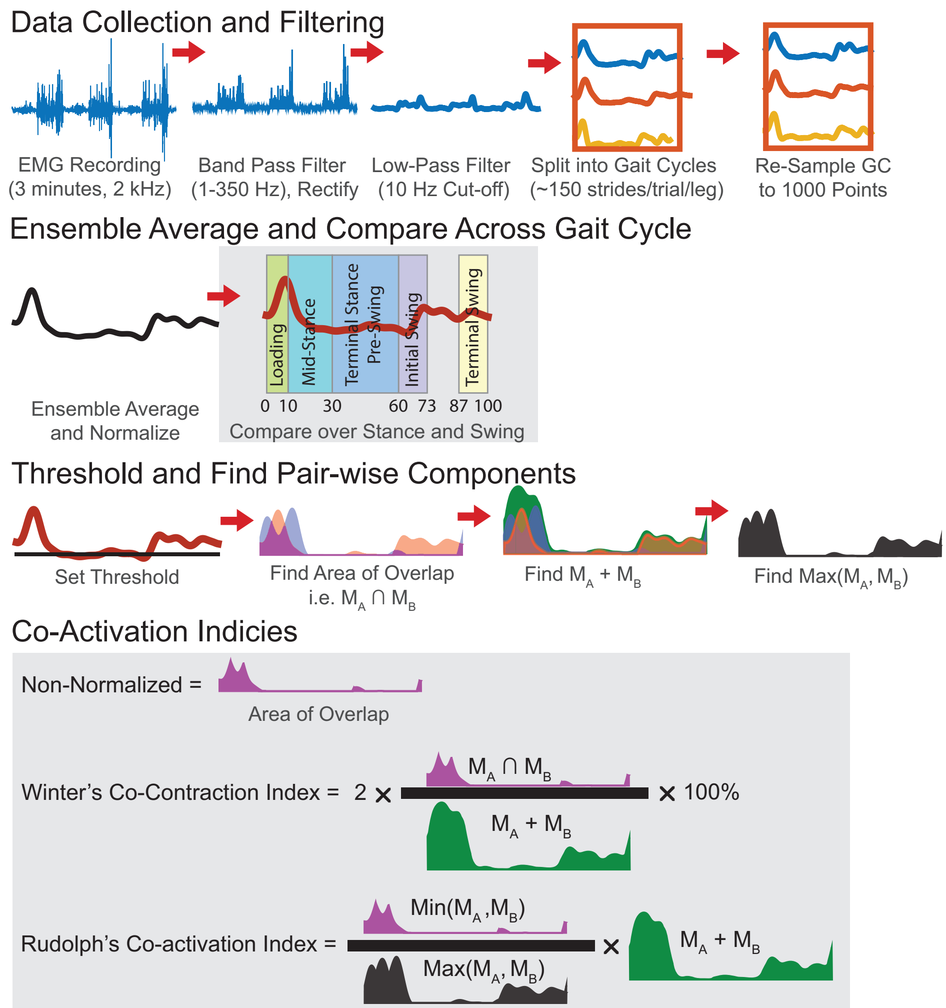



Figure 3.2: Visual description of how EMG data was processed for each type of comparison: ensemble average group traces and various co-activation indicies.

Young adults had no significant changes in any formulation of the co-activation index for either gait challenge compared to normal walking (Figure 3.5. However, they show a trend toward higher co-activation using the Rudolph formulation in the MG-TA pair for the visual trial compared to normal ($p = 0.099$).

## Old Condition Effects

Old adults exhibited an increase in MH activity compared to normal walking in the visual trial across all five phases of gait ($p$‘s $\leq 0.036$). They had an increase in VL activity during

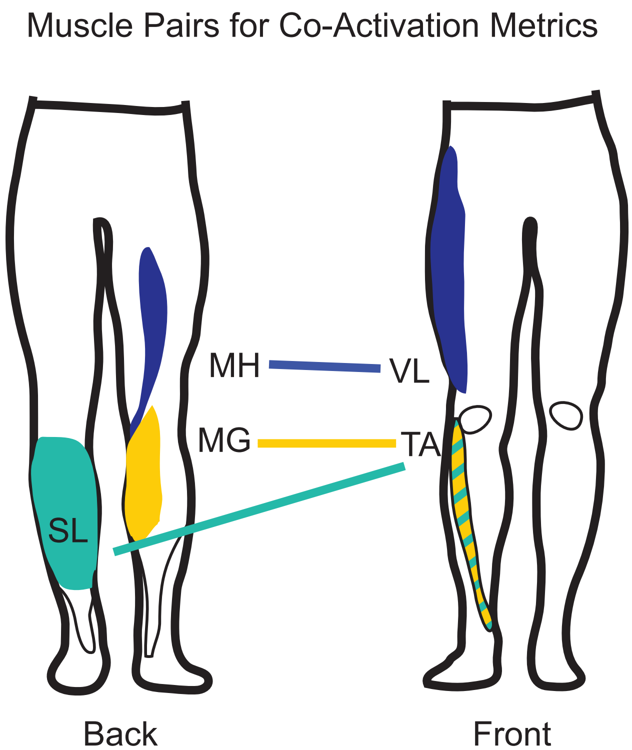



Figure 3.3: Illustration of the muscles used in co-activation metrics. The semitendinosis (MH, medial hamstring) was paired with vastus lateralis (VL). Soleus (SL) and medial gastrocnemius (MG) were both compared to tibialis anterior (TA).

the visual versus normal trial during loading response ($p = 0.049$), mid-stance ($p = 0.023$), and terminal swing ($p = 0.004$). Old adults also had MG activity in the visual trial that was significantly different from normal in mid-stance ($p = 0.005$), initial swing ($p = 0.018$), and terminal swing ($p < 0.001$); they also had a tendency to have increased MG activity in loading response ($p = 0.070$) in the visual trial. Soleus activity in the visual trial in old adults was significantly increased compared to normal walking in loading response ($p = 0.007$), mid-stance ($p < 0.001$), and initial swing ($p < 0.001$); it tended to be elevated in terminal swing ($p = 0.075$). Finally for TA, old adults had significantly increased activity in visual vs. normal conditions during mid-stance ($p = 0.010$) and terminal stance/pre-swing ($p = 0.006$). If the correction for a positive Levene's test for the normal trial is taken into account, TA activity is also significantly different from normal in the visual trial during terminal swing ($p = 0.002$), otherwise it is not significant.

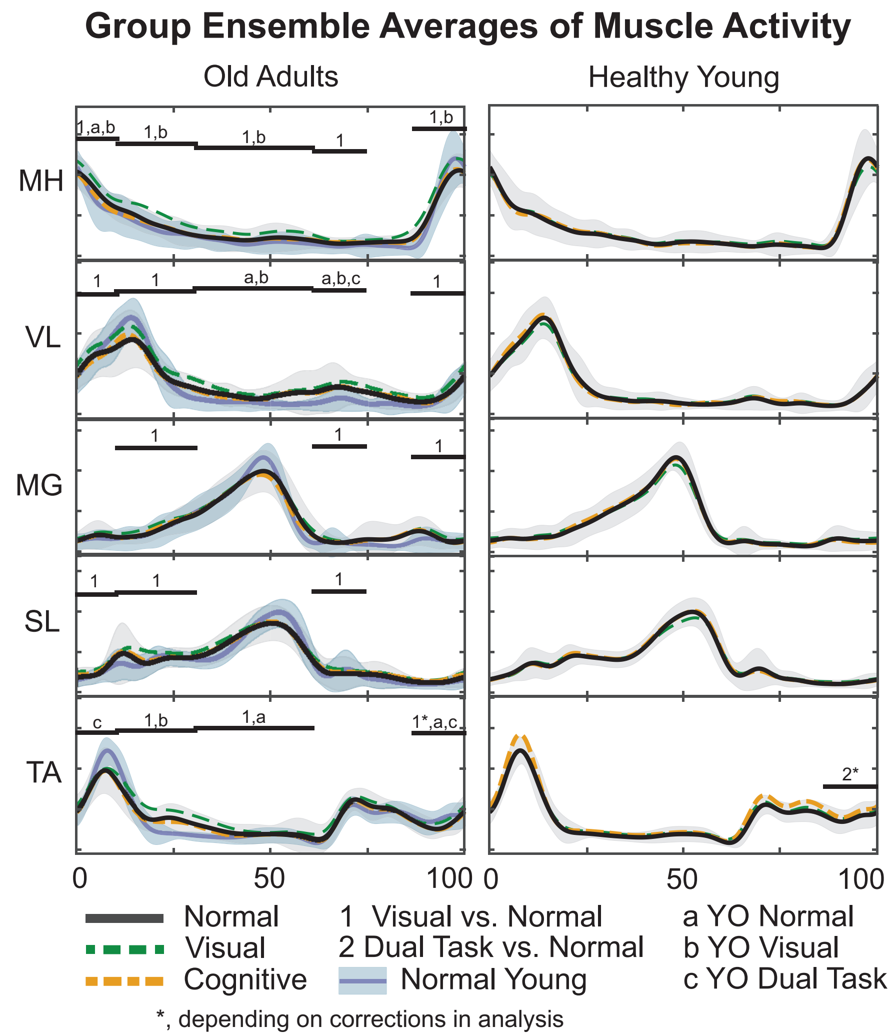



Figure 3.4: Ensemble averaged traces of muscle activation for each trial and group. For the old adults, the blue line and blue shading represent the normal trial for young adults.

Old adults had increased muscle co-activation in the visual trial using the un-normalized co-activation index for all three muscle pairs: medial hamstring-vastus lateralis, medial gastrocnemius-tibialis anterior, and soleus-tibialis anterior (p‘s≤0.006). They also had increased co-activation in MH-VL ($p = 0.012$) and SL-TA ($p = 0.014$) during the visual trial compared to normal using the Winter co-activation index. The Rudolph formulation also yielded significant increases in co-activation of all three muscle pairs (p‘s≤0.033).

Table 3.1: Group mean (± standard deviation) values for SW, SL, SWV, and SLV during each condition are listed for old and young adults walking at preferred speed. Group and condition main effects or interactions from a repeated measures ANOVA are reported.

| Phase of Gait Cycle | Muscle | Normal | | Visual | | Cognitive | | $p$ Values | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Old | Young | Old | Young | Old | Young | Age | Condition | Age × Condition |
| Loading Response (0-10%) | MH | 1.64 (0.06) | 1.46 (0.07) | 1.85 (0.09) | 1.43 (0.11) | 1.51 (0.07) | 1.40 (0.08) | **0.023** | **0.002** | **0.007** |
| | VL | 1.41 (0.08) | 1.49 (0.09) | 1.64 (0.11) | 1.44 (0.12) | 1.36 (0.11) | 1.58 (0.13) | 0.783 | 0.312 | **0.003** |
| | MG | 0.37 (0.04) | 0.32 (0.05) | 0.44 (0.04) | 0.34 (0.05) | 0.37 (0.04) | 0.31 (0.05) | 0.268 | **0.007** | 0.476 |
| | SL | 0.51 (0.04) | 0.48 (0.04) | 0.61 (0.05) | 0.46 (0.06) | 0.55 (0.06) | 0.47 (0.06) | 0.199 | 0.160 | **0.024** |
| | TA | 1.61 (0.06) | 1.85(0.07) | 1.69(0.10) | 1.87 (0.12) | 1.59 (0.14) | 2.14 (0.17) | **0.011** | 0.362 | 0.116 |
| Mid-Stance (10-30%) | MH | 0.82 (0.05) | 0.71 (0.05) | 1.09 (0.06) | 0.75 (0.07) | 0.79 (0.05) | 0.74 (0.06) | **0.025** | <**0.001** | <**0.001** |
| | VL | 1.28 (0.05) | 1.42 (0.06) | 1.52 (0.09) | 1.33 (0.11) | 1.28 (0.08) | 1.41 (0.10) | 0.782 | 0.306 | **0.007** |
| | MG | 0.55 (0.04) | 0.55 (0.04) | 0.66 (0.04) | 0.59 (0.05) | 0.57 (0.05) | 0.58 (0.06) | 0.676 | **0.006** | 0.172 |
| | SL | 0.84 (0.04) | 0.80 (0.05) | 1.01 (0.06) | 0.83 (0.07) | 0.87 (0.06) | 0.82 (0.07) | 0.223 | **0.002** | **0.030** |
| | TA | 0.92 (0.04) | 0.78 (0.05) | 1.16 (0.07) | 0.82 (0.08) | 0.86 (0.07) | 0.85 (0.08) | 0.055 | <**0.001** | <**0.001** |
| Terminal Stance and pre-swing (30-60%) | MH | 0.43 (0.04) | 0.35 (0.05) | 0.59 (0.05) | 0.38 (0.06) | 0.43 (0.04) | 0.34 (0.04) | **0.036** | <**0.001** | **0.010** |
| | VL | 0.49 (0.03) | 0.30 (0.04) | 0.59 (0.05) | 0.33 (0.06) | 0.47 (0.03) | 0.29 (0.04) | <**0.001** | **0.014** | 0.366 |
| | MG | 1.42 (0.03) | 1.45 (0.04) | 1.46 (0.06) | 1.37 (0.06) | 1.37 (0.06) | 1.45 (0.06) | 0.888 | 0.694 | **0.040** |
| | SL | 1.35 (0.04) | 1.39 (0.05) | 1.41 (0.04) | 1.34 (0.05) | 1.35 (0.05) | 1.41(0.05) | 0.809 | 0.888 | 0.060 |
| | TA | 0.42 (0.03) | 0.33 (0.04) | 0.52 (0.04) | 0.38 (0.05) | 0.40 (0.04) | 0.38 (0.04) | 0.100 | <**0.001** | **0.009** |
| Initial Swing (60-73%) | MH | 0.33 (0.03) | 0.26 (0.03) | 0.41 (0.04) | 0.32 (0.04) | 0.35 (0.03) | 0.26 (0.04) | 0.063 | **0.002** | 0.790 |
| | VL | 0.61 (0.07) | 0.33 (0.08) | 0.73 (0.08) | 0.38 (0.09) | 0.60 (0.07) | 0.35 (0.08) | **0.008** | **0.006** | 0.182 |
| | MG | 0.28 (0.04) | 0.23 (0.04) | 0.34 (0.05) | 0.28 (0.05) | 0.27 (0.04) | 0.23 (0.04) | 0.380 | <**0.001** | 0.755 |
| | SL | 0.54 (0.06) | 0.55 (0.06) | 0.65 (0.06) | 0.58 (0.07) | 0.57 (0.06) | 0.54 (0.07) | 0.739 | <**0.001** | 0.147 |
| | TA | 0.69 (0.03) | 0.62 (0.04) | 0.81 (0.05) | 0.72 (0.06) | 0.67 (0.06) | 0.78 (0.07) | 0.817 | **0.013** | **0.024** |
| Terminal Swing (87-100%) | MH | 1.44 (0.06) | 1.50 (0.07) | 1.75 (0.08) | 1.42 (0.09) | 1.46 (0.06) | 1.53 (0.07) | 0.454 | **0.024** | <**0.001** |
| | VL | 0.48 (0.04) | 0.43 (0.04) | 0.63 (0.05) | 0.45 (0.06) | 0.47 (0.04) | 0.43 (0.05) | 0.134 | **0.006** | **0.034** |
| | MG | 0.35 (0.04) | 0.29 (0.04) | 0.44 (0.04) | 0.33 (0.05) | 0.36 (0.04) | 0.26 (0.04) | 0.130 | <**0.001** | 0.198 |
| | SL | 0.27 (0.02) | 0.24 (0.02) | 0.35 (0.04) | 0.29 (0.04) | 0.32 (0.04) | 0.24 (0.05) | 0.249 | **0.024** | 0.512 |
| | TA | 0.63 (0.04) | 0.78 (0.04) | 0.75 (0.05) | 0.85 (0.06) | 0.61 (0.07) | 0.91 (0.08) | **0.008** | 0.090 | 0.051 |

Table 3.2: Group mean (± standard deviation) values for SW, SL, SWV, and SLV during each condition are listed for old and young adults walking at preferred speed. Group and condition main effects or interactions from a repeated measures ANOVA are reported. Abbreviations: Non-Normalized (NN), Winter's Formulation (Wn), Rudolph's Formulation (Rd).

| Metric | Group | Normal | Visual | Cognitive | Effect | *DoF* | *F* | *p* |
|---|---|---|---|---|---|---|---|---|
| MHVL (NN) | Old | 21.0 (2.3) | 41.6 (4.1) | 20.5 (2.1) | Age | 1,26 | - | 0.234 |
| | Young | 21.4 (2.6) | 27.9 (4.8) | 20.2 (2.5) | Condition | 2,52 | 25.53 | <**0.001** |
| | | | | | Age × Condition | 2,52 | 6.15 | **0.004** |
| MGTA (NN) | Old | 15.7 (1.3) | 22.9 (2.6) | 14.6 (1.2) | Age | 1,26 | 9.54 | **0.005** |
| | Young | 9.3 (1.5) | 12.8 (3.0) | 10.7 (1.4) | Condition | 2,52 | 8.59 | <**0.001** |
| | | | | | Age × Condition | 2,52 | - | 0.119 |
| SLTA (NN) | Old | 19.4 (1.8) | 30.1 (3.4) | 19.6 (2.1) | Age | 1, 26 | 5.94 | **0.022** |
| | Young | 12.9 (2.1) | 16.4 (4.0) | 14.8 (2.4) | Condition | 2. 52 | 11.40 | <**0.001** |
| | | | | | Age × Condition | 2. 52 | 4.37 | **0.018** |
| MHVL (Wn) | Old | 48.2 (3.8) | 58.0 (3.6) | 46.1 (3.9) | Age | 1,26 | - | .968 |
| | Young | 48.8 (4.4) | 55.3 (4.1) | 47.5 (4.5) | Condition | 2, 52 | 12.07 | <**0.001** |
| | | | | | Age × Condition | 2, 52 | - | 0.599 |
| MGTA (Wn) | Old | 30.0 (2.4) | 36.6 (4.1) | 29.0 (2.2) | Age | 1,26 | 8.43 | **0.007** |
| | Young | 18.23 (2.8) | 24.2 (4.7) | 19.4 (2.6) | Condition | 2, 52 | 5.58 | **0.006** |
| | | | | | Age × Condition | 2, 52 | - | 0.791 |
| SLTA (Wn) | Old | 36.6 (3.6) | 45.7 (4.9) | 36.0 (3.4) | Age | 1, 26 | 4.63 | **0.041** |
| | Young | 25.3 (4.2) | 30.3 (5.6) | 26.3 (3.9) | Condition | 2, 52 | 7.87 | **0.001** |
| | | | | | Age × Condition | 2, 52 | - | 0.351 |
| MHVL (Rd) | Old | 32.4 (3.5) | 67.9 (7.5) | 30.1 (3.5) | Age | 1,26 | - | .186 |
| | Young | 29.6 (4.1) | 44.8 (8.6) | 29.9 (4.0) | Condition | 2, 52 | 27.55 | <**0.001** |
| | | | | | Age × Condition | 2, 52 | 4.82 | **0.027** |
| MGTA (Rd) | Old | 22.6 (1.9) | 33.3 (4.5) | 20.9 (1.8) | Age | 1,26 | 9.05 | **0.006** |
| | Young | 12.3 (2.2) | 19.1 (5.2) | 14.3 (2.1) | Condition | 2, 52 | 7.25 | **0.002** |
| | | | | | Age × Condition | 2, 52 | - | 0.350 |
| SLTA (Rd) | Old | 29.2 (3.2) | 46.6 (6.4) | 29.3 (3.4) | Age | 1, 26 | 5.44 | **0.028** |
| | Young | 17.6 (3.6) | 24.8 (7.4) | 20.4 (4.0) | Condition | 2, 52 | 9.85 | **0.003** |
| | | | | | Age × Condition | 2, 52 | - | 0.121 |

## Young vs. Old Adults

Young and old adults had significantly different MH activity during the loading response phase of normal walking ($p = 0.033$). They also differed significantly in MH activity during loading response ($p = 0.014$), mid-stance ($p = 0.003$), terminal stance/pre-swing ($p < 0.001$), and terminal swing ($p = 0.035$). MH activity tended to be different between young and old adults during terminal stance/pre-swing ($p = 0.057$).

For VL, young and old adults differed significantly in normal walking during terminal stance/pre-swing ($p = 0.044$) and initial swing ($p = 0.002$) and tended to be different in

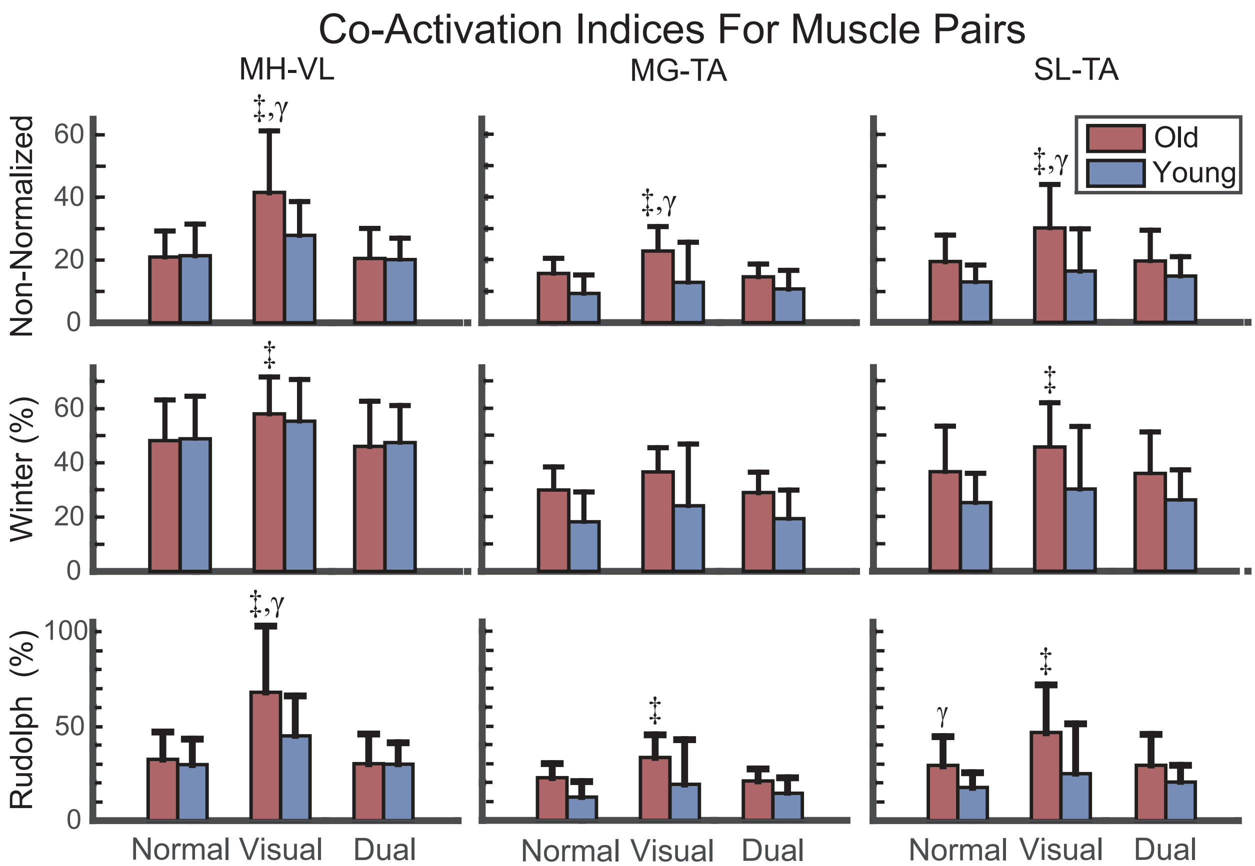



Figure 3.5: Co-activation indices using non-normalized and normalized formulations for young and old adults. Significant results ($p < 0.05$) are denoted for condition effects (‡) and age effects ($\gamma$).

mid-stance ($p = 0.063$). Old adults had significantly higher VL activity than young adults in terminal stance/pre-swing ($p = 0.002$) and initial swing ($p < 0.001$). They differed significantly for the dual-task condition in initial swing ($p = 0.003$) and tended to be different in terminal stance/pre-swing ($p = 0.071$).

TA activity tended to differ between groups in the normal trial during terminal stance/ pre-swing ($p = 0.031$) and terminal swing ($p < 0.001$). Old adults had higher TA activity than young adults in the visual trial during mid-stance ($p < 0.001$). They also differed significantly in the dual-task condition during terminal swing ($p = 0.014$) and loading response ($p = 0.035$).

There were no differences between young and old adults for the Winter co-activation index. However, the non-normalized index revealed an increase in co-activation of all three muscle pairs in old adults compared to young adults ($p$‘s$\leq$0.023) during the visual trial. Using the Rudolph formulation, old adults had significantly greater SL-TA co-activation during normal walking ($p = 0.001$) and tended to have higher co-activation during the visual ($p = 0.058$) and dual-task ($p = 0.065$) trials compared to young adults.

## 3.5 Discussion

Overall, the results did not entirely support the hypotheses of this study. While old adults showed some increases in muscle activity at various points of the gait cycle during normal walking compared to young adults, the only co-activation index that showed a significant age difference in normal walking was the Rudolph formulation for the SL-TA pair. That said, the visual condition did produce significant increases in both muscle activation and the co-activation indices nearly across the board in old adults, though only some formulations resulted in significant age effects. The responses of both groups to the dual-task condition was more similar to normal walking than the visual condition in that there were age group differences in activation at various points in the gait cycle, but no differences in co-activation indices.

In general, young adults seemed unaffected by the gait challenges in this study. There are two possible explanations for this result. The first possibility is that young adults have the cognitive capacity and mental flexibility to adjust which sensory information they use for balance maintenance (visual trial) or to perform a secondary task while walking. As such, the young adults may have perceived the challenges as being a low-threat to their balance. The other explanation is that old adults in the study made a global adjustment, similar to anticipatory postural adjustments, to muscle co-activation to stiffen their limbs as a means of preparing for perceived threats to balance. In contrast, young adults were using a more reactive or reflexive strategy to cope with challenges to balance. As such, these adjustments would appear as more transient changes in muscle activation that would not suggest a persistent change in muscle coordination.

In contrast to young adults, old adults were primarily affected by inaccurate visual feedback, with subjects showing increased muscle activation throughout the gait cycle as well as increases in the co-activation indices. The old adults in this study were largely unaffected by dual-task walking. They showed no significant changes in muscle activation or the co-activation indices compared to normal walking. They did show increased activation of the VL muscle during terminal stance/pre-swing. Further, old adults had lower TA activation than young adults during terminal swing and loading response for the dual-task trial, though this was primarily due to an (insignificant) increase in young adult TA activity during this trial. Old adult TA activity is virtually indistinguishable between the normal and dual-task trials.

These results support the idea proposed in our previous work that old adults may be more reliant on visual information to maintain their balance than are young adults [74, 64]. In these prior studies, we found that visual perturbations affected gait variability more than a dual-task condition. There is some evidence that increased visual reliance may be a compensatory mechanism for age-related deterioration of somatosensory feedback [49] and vestibular function [12]. Clinically, this suggests that accurate visual information is paramount for old adults' balance control during gait. Further, there is evidence that old adults may more specifically rely on peripheral vision for balance [48]. In this study, the portion of the hallway that appeared nearer was in subjects' peripheral vision and moved with the greatest amplitude, while the more central end of the hallway moved very little. Hence, young adults may have been better able to reject the motion of the near hallway by relying more on central vision and focusing on the end of the hallway. Old adults may have been unable to make this switch and therefore were affected by the full motion of the near portion of the hallway.

If co-activation functions as a protective mechanism to maintain balance in challenging environments [18], a change in co-activation may indicate a change in an individual's perception of their balance. In this study, the physical environment subjects walked in did not change. All trials were performed on the same treadmill with the same lighting conditions and harness system. The only differences between trials were whether we asked subjects to perform serial seven subtractions or provided them with different visual feedback. Therefore, there was nothing in the physical environment that provided an actual threat to subjects' balance, only their perception of a threat due to inaccurate visual feedback about their environment. In prior studies, Okada et al. and Nagai et al. found that individuals with a fear of falling exhibited Plantarflexor-Dorsiflexor co-activation of roughly 55% (using the Winter formulation [75]) while those without such fear were closer to 45% during perturbed platform walking and normal walking, respectively [72, 73]. In the second study, researchers used the Tinetti Falls Efficacy Scale (FES) to determine which subjects had any fear of falling (score $> 10$, the minimum) [73, 77]. In the present study, FES scores were recorded for six old adults who reported experiencing a fall in the past year. Of these, only one subject reported a score greater than 10, making any link between FES score and levels of co-activation in the present study tenuous at best. The subject who reported an elevated FES score did have some elevation in muscle co-activation but it was by no means substantially different from other old adults.

Further work is needed to understand the information contained in different muscle co-activation indices. In the present study, the indices used agreed in some cases but not in others. For example, using the Winter formulation, the pair of muscles could increase their activation substantially with only a minimal effect on (or even a reduction in) the co-activation index. On the other hand, the Rudolph formulation would tend to increase with an increase in activity of both muscles because the sum of the two muscles will always be equal to or greater than the most active muscle. The non-normalized formula would also increase as both muscles increase activation because it is driven entirely by the muscle with lower activation.

In summary, we have shown that while muscle activation differences exist between old and young adults in normal walking, activation and co-activation increase substantially in old adults in the presence of inaccurate visual information. This dramatic effect was not seen when subjects were asked to perform serial seven subtraction. Further work is needed to understand the role of vision in falls among community-dwelling old adults.

# Chapter 4

# Cranial Nerve Non-Invasive Neuromodulation (CN-NINM): A pilot study of the effectiveness of using neuromodulation to enhance gait and postural balance in old adults.

## 4.1 Abstract

*Falls represent a significant and costly cause for adults over age 65 to seek medical treatment. While much work has been done to understand the causes of falls in old adults, it remains challenging to implement simple, effective interventions that can mitigate fall risk. Neuromodulation remains a largely unexplored area for intervention in gait and balance, in large part because non-invasive techniques that can be ethically deployed in non-terminal pa-*

*tients are still relatively new. The purpose of this study was to investigate the efficacy of one such non-invasive technique - cranial nerve non-invasive neuromodulation (CN-NINM) in improving gait and balance in relatively healthy old adults. In order to evaluate the efficacy of the technique, a variety of clinical and quantitative gait and balance metrics were used, including the dynamic gait index, sensory organization test, the three-minute walk test, gait variability, and posturography. Sixteen old adults were randomly assigned a portable neuromodulation stimulator (PoNS ®) that delivered either active (age: 71 ± 5.6 years, 8 females) or sub-threshold ( 70.3 ± 3.3 years, 7F/1M) electrical stimulation. All subjects participated in ten supervised walking and balance training session with an investigator who was blinded to their group assignment. A group of twelve young adults (23.6 ± 3.9 years, 7F/5M) was evaluated for comparison. After the intervention, subjects exhibited reduced step width variability when subjected to visual perturbations during walking. Further, there were some significant reductions in standing sway measures. However, there were no significant differences in post-training metrics between the active and control groups. It is noted that the subjects who participated were generally relatively healthy and physically active with limited history of falling. Future studies should consider the potential benefits of CN-NINM in older adults with a fall risk, given their greater potential for improvement.*

## 4.2 Introduction

Fall risk in adults increases substantially with advancing age. In particular, falls are both prevalent and costly in adults over 65 years of age. Since the 1980's, the National Institutes of Health have invested heavily in research surrounding the causes of falls in old adults, prevention strategies and rehabilitation of gait and balance in this population.

Physiologically, old adults show changes in sensory acuity [11, 12], muscle strength [13, 14], neuromuscular function [13], cognitive capacity [15], and executive function [16]. These changes may make it difficult for old adults to assess their level of stability and make corrections quickly, causing them to adopt more broad-based balance strategies such as a more cautious gait pattern or increased muscle co-activation [51].

Fall prevention strategies have largely focused on changing external factors that affect fall risk. Things like reviewing medications for combinations known to increase dizziness and ensuring that individuals are able to see clearly via eye exams and vision correction are common practice. Further, modifying home environments to remove tripping hazards and adding grab bars to areas where falls are common (e.g. in the bathroom) is an additional step that may be implemented. Regular exercise is also encouraged to promote muscle strength and coordination as well as physical fitness, joint health and endurance.

In the late 1980s and early 1990s, the NIH funded a number of falls prevention studies focused on exercise interventions, the FICSIT trials [5, 6]. Studies focused on activities ranging from muscle strength to aerobic exercise to Tai Chi. However, most of these programs showed only modest effects on the incidence of falls among the study populations [5, 6, 7, 8, 9, 10]. Further, a more recent study found no clinically or statistically significant changes in individuals with a history of falls following four months of physical exercises and rehabilitation [22].

Since fall risk is multi-factorial, a number of methods can be employed to assess it. Clinically, qualitative metrics such as the Berg Balance Scale [78, 34] and the Dynamic Gait Index [33] can be used by trained physicians and physical therapists with good reliability. Further, given the link between cognition and falls, a variety of cognitive tests may be used to assess various aspects of individuals' mental state and function. These tests can include the Mini-Mental State Exam, the Trailmaking Test Parts A and B, etc. In addition self- or care giver- reported ability to perform activities of daily living (ADL's) can give insight into individuals' balance ability in their normal environment [77]. More quantitatively, computerized posturography tests such as the sensory organization test (SOT) can provide information about more subtle changes in standing balance [79].

In research settings, changes in gait variability have been linked to fall risk in old adults

[37, 35]. Variability is most commonly quantified as either the standard deviation or coefficient of variation of stride time, step width or step length over many steps. Step width variability may be particularly indicative of balance during walking because the mediolateral direction is inherently unstable during walking and requires fine motor control of foot placement from step to step [41] to maintain balance. In relatively healthy old adult populations, gait variability is frequently indistinguishable from healthy young adults during normal, unencumbered walking. Thus adding an extra challenge to walking is often required to detect differences between old and young adults. Typically, the most effective challenges target systems that show age-related changes by altering sensory input [46, 41, 50], adding an attention-demanding cognitive task [44, 43], or altering the physical requirements of walking (e.g. changing a spatiotemporal aspect of gait or navigating around obstacles) [47, 40]. Recently, we showed that gait variability metrics in healthy old adults increase markedly in the presence of visual perturbations, an effect which may be indicative of over-reliance on vision to plan step placement [74, 64].

While conventional exercise and rehabilitation have shown limited efficacy in reducing fall risk, a more recent area of investigation has been the use of neuromodulation either as a stand-alone treatment or to enhance more conventional rehabilitation. Neuromodulation seeks to use either a drug or device to suppress or enhance neural activity for treatment purposes. The most well-known form of neuromodulation is deep brain stimulation (DBS) which is used primarily in Parkinson's disease patients who have run out of other treatment options [23]. This restriction stems largely from the way that this technique is implemented - by surgically implanting electrodes near the basal ganglia. In general this approach is effective for reducing resting tremor, but has not shown much efficacy in improving gait or balance [80]. A less invasive option is transcranial magnetic stimulation (TMS) which uses magnetic pulses to stimulate regions of the brain. In general, TMS tends to stimulate larger regions of the brain and has not been shown effective in rehabilitation of gait or balance [24, 25].

Cranial nerve non-invasive neuromodulation (CN-NINM) is a targeted, non-invasive form of brain stimulation that was developed in the early 2000's. This approach to neuromodulation uses a small device (Figure 4.1) to deliver electrical stimulation to the brain via cranial nerve endings in the tongue. Previous work with this technique has revealed changes in brain activation patterns on fMRI in response to an optical flow stimulus. These changes seem to localize in regions associated with movement, balance, and resolving conflicts between neural signals from different systems [30, 81]. The CN-NINM approach utilizes 20-minute sessions of stimulation combined with rehabilitation exercises such as walking or balance training and has shown promise for improving clinical metrics of gait and balance in individuals with vestibular loss [29, 53], multiple sclerosis[27, 28], and traumatic brain injury [26]. To date, this technique has not been investigated for efficacy in old adults at risk of falling who have no concurrent neurological diagnosis.


Figure 4.1: Portable Neuromodulation Stimulator used to deliver Cranial Nerve Non-Invasive Neuromodulation

The purpose of this study was to investigate the efficacy of the CN-NINM approach to improve walking and balance in relatively healthy old adults. We hypothesized that old adults receiving gait and balance training with active CN-NINM stimulation would show greater improvement in step width variability, postural balance, and clinical metrics of fall risk than subjects receiving the same training with placebo stimulation.

## 4.3 Methods

In this study, young and old adults underwent the same evaluations. Twelve young adults (age: 23.6 $\pm$ 3.9 years, height:1.69 $\pm$ 0.25m, mass: 70.7 $\pm$ 11.3 kg, 7 female) participated in baseline evaluations that were used to establish healthy normal results for comparison to the old adults in the study. Sixteen old adults (70.7 $\pm$ 4.5 years, 1.65 $\pm$ 0.05 m, 69.7 $\pm$ 11.1 kg, 15 female) participated in a 10-day gait and balance intervention using either active or control (1000 times below sensory threshold) CN-NINM stimulation and were evaluated before and after the intervention. Group assignment was randomized and the investigator administering the rehabilitation sessions was blinded to group membership. Among old adults, ten reported no falls in the previous year, while six had experienced at least one fall. Of the six that had fallen, two met our definition of a "faller" - meaning that they reported falling in the last year and had a DGI score $\leq$ 19.

### Device Assignment

Old adults were assigned a device for use during the study following their initial evaluation. The investigators who assigned subjects to either the active or control group and went through initial device assignment with subjects also assisted with data collection during evaluations but was not involved in the gait and balance training portion of the study or with primary data analysis. With each subject, the investigators went through a standardized process of setting the level of stimulation on the device and recorded the settings to be used in subsequent training sessions. For subjects in the active group, the stimulation level was set between the thresholds for sensation and discomfort. Subjects in the control group were receiving electrical stimulation, but at a level that was roughly 1000 times below the sensory threshold. While investigators still went through an identical process of "adjusting" stimulation level with control subjects, the devices used were set so that the buttons that adjust stimulation level were disabled.

## Clinical Metrics

Clinical metrics included the Dynamic Gait Index (DGI) [33] and the Sensory Organization Test (SOT) [79]. Further, Trailmaking Part B and the Semmes-Weinstein test are all clinically-based tests. The DGI is an eight item walking test consisting of tasks such as walking and turning one's head, changing speed, and stair climbing. Subjects were scored on each item by a physical therapist with each item receiving between zero (could not complete) and three (completed with no visible instability) points. The maximum score on the DGI is 24 and anyone scoring $\leq$19 is considered at increased risk of falling [33] and a 3-point change is considered clinically significant [82].

The SOT is a computerized posturography test consisting of three 20-second trials for each of six conditions [79]. Subjects wear a harness and stand on a force plate with their feet in a standardized position based on height. During different conditions, subjects are instructed to open or close their eyes and informed that the walls or floor may move. During trials with the floor and/or walls moving, the respective component tracks with the subjects' center of pressure movement to maintain either the subject's ankle angle and/or the distance from the subject's eyes to the wall. This forces subjects to rely on other sensory information to sense sway. For example, when the walls move, subjects must rely on somatosensory and vestibular information to maintain their balance. Subjects receive numerical scores (0-100) based on center of pressure movement during each trial, where a 0 typically represents a fall and 100 represents no movement of the COP, with a final composite score given at the end. The software also automatically compares subjects' scores to age-matched norms with "green" and "red" bars indicating above and below age-related averages. An 8-point change in SOT score is considered the minimum detectable change [82] based on a test of thirteen young adults tested two days apart.

Trailmaking Part B (TMT B) is used as a test of executive function. Subjects are asked to draw a line through an alternating sequence of numbers and letters (i.e. 1-A-2-B-3-C) scattered on a page while being timed. Alternating between letters and numbers requires subjects to switch tasks instead of simply finding the next item in a simple sequence. Longer time-to-completion may indicate executive function decline and has been tied to fall risk [83].

The 3-minute walk test is a variation of the 2-minute and 6-minute walk tests. The premise is that subjects are asked to walk "as far as possible" in the allotted time. Typically this test is administered with patients who have significant impairments such that they may not be able to walk the entire time and may stop to rest partway through. For older adults, a change of 12.2 meters on the 2-minute test [84] or a change of 58.21 m on the 6-minute version [85] are considered the minimum detectable change. Extrapolating from these, we considered a change of 18 m to be a marginal change and 29 m to be a substantial change for the 3-minute walk test.

Six of the old adult subjects also completed a somatosensory function test using the Semmes-Weinstein monofilament test. Monofilaments of various thicknesses (and therefore bending strengths) were used to probe four defined points (first phalanges and 1st, 3rd and 5th metatarsal head) on the plantar surface of each foot. The bending strength of the smallest consistently detectable monofilament at each point was recorded.

## Quantitative Metrics

For quantitative gait testing, we focused on variability of step width and step length, as well as muscle coordination, while subjects walked on a instrumented split-belt treadmill down a virtual hallway in a motion capture environment (Figure 4.2). Subjects walked on the treadmill at their preferred overground walking speed. A semi-circular rear-projection screen surrounded the front half of the treadmill and took up most of subjects' visual field. On this screen, we projected a virtual hallway that moved at the same speed as the treadmill. We used a Motion Analysis (Santa Rosa, CA) passive motion capture system to record markers placed on subjects' shoulders, pelvis, knees, ankles, and heels. Further marker clusters on plates were strapped to subjects' thighs and shanks to improve limb tracking. Motion of the

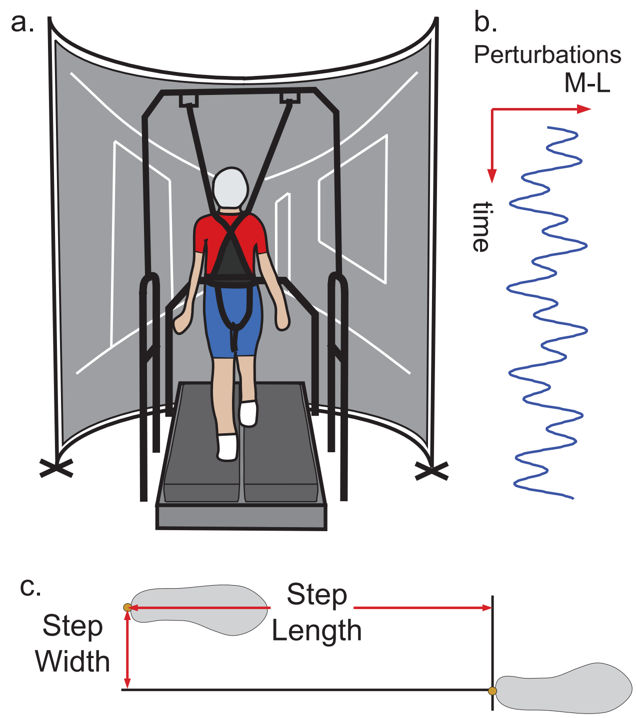



Figure 4.2: Experimental setup. 1a. Subject walks on a split-belt treadmill surrounded by a semi-circular projection screen. A rear-projected virtual hallway moved at the same speed as the treadmill. Old adults wore a harness during testing that was adjusted to prevent falls but still allow free movement around the treadmill surface. 1b. During the visual perturbation trial, we added a mediolateral perturbation consisting of a sum of sinusoids to the virtual hallway motion. 1c. Step width and step length were calculated from heel kinematic data for both left-right and right-left steps.

S2 and heel markers were used to calculate the length and width of each step in a trial. Then for each subject the mean (SL, SW) and standard deviation (SLV, SWV) were computed for each trial and averaged across each group.

Subjects performed one three-minute walking trial for each of four conditions: normal, visually perturbed, dual task, and narrow step width. Normal walking consisted of single-task walking in the virtual hallway. During the visually perturbed trial, the hallway moved in the medio-lateral direction according to $0.175(sin(0.135\pi t) + (sin(0.442\pi t)))$ meters in addition to the normal fore-aft movement. For the dual-task trial, subjects were asked to perform serial seven subtraction [35] starting at a three-digit number between 500 and 800, if subjects got to zero before the end of the trial, they were given another 3-digit number to continue from. Finally for the narrow step width trial, subjects were instructed to "walk on a line" with the small gap between treadmill belts suggested as a guide. Subjects were allowed to look at their feet rather than the virtual hallway for this trial.

Subjects also completed two sixty-second posturography trials (AMTI BP400600 force-plates, Watertown, MA) with eyes open and eyes closed while standing with their feet on separate force plates. Standard center of pressure (CoP) posturography metrics were quantified including the 95% ellipse area, CoP range, maximum and RMS CoP velocity, and CoP path length were computed for each trial.

## Statistical Analysis

We first confirmed normal distribution of data for the SOT, TMT B, 3-minute walk, posturography and gait variability data using a Kolmogorov-Smirnov test (STATISTICA, StatSoft, Tulsa, OK). For all analyses, the active and control groups were compared to each other both before the intervention and after the intervention and to themselves on a pre-post basis. Both groups were also compared to young adults, as were the overall combined old adult groups before and after the intervention.

Some of the posturography data was not normally distributed. For the portion that was normally distributed, one-way ANOVAs were used to assess group and eyes open/closed conditions. Unequal N post-hoc tests were used for pair-wise comparisons. For those that were not normally distributed, a Wilcoxon matched pairs test was used to compare eyes open to eyes closed for each group and Mann-Whitney tests were used to compare groups in a pair-wise fashion for each parameter.

For the SOT, TMT B, and the3-minute walk test, we used a one-way ANOVA with an Unequal N post-hoc test to test for significant effects of group membership and make pair-wise comparisons, respectively. These analyses focused on differences between groups.

For gait variability data, we used a repeated measures ANOVA with an Unequal N post-hoc test to investigate significant effects and interactions of age (old vs. young) and condition (normal, cognitive, visual, narrow). Corrections for heterogeneous variances were used when necessary, as determined from Levene's Test. We focused on variability on the same task when comparing groups and evaluated the effects of different walking conditions within groups.

## Intervention

While using the assigned active or control PoNS device, old adults participated in ten daily one-hour balance and gait training sessions on consecutive days. Balance training (20 minutes per session) consisted of subjects standing quietly under progressively more difficult foot placement and surface conditions (Figure 4.3a). Particular attention was given to reducing sway, standing up straight, maintaining alignment of ears, shoulders, hips, knees and ankles in the sagittal plane and good symmetry in the frontal plane. Gait training (20 min per session) on a treadmill was divided into 5-minute blocks, each with a specific attentional focus (Figure 4.3b). The main foci in gait training were left-right symmetry and correcting abnormal movement patterns (e.g., lack of pelvic rotation, minimal push-off, shuffling gait, Trendelenburg gait, or irregular weight transitions).

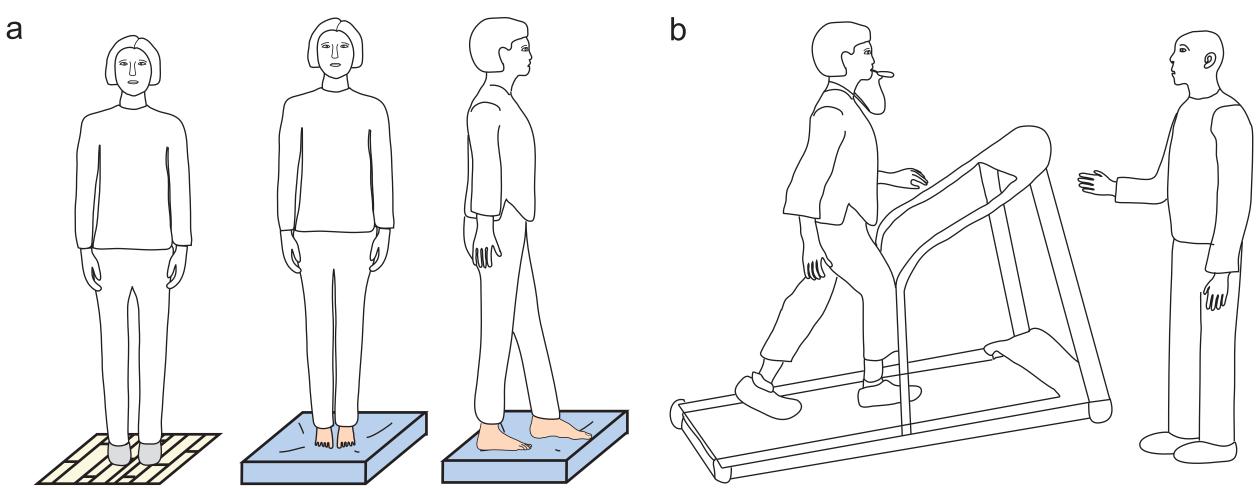



Figure 4.3: Old Adult subjects underwent ten gait and balance training sessions with active or control CN-NINM. Sessions focused on normalizing gait kinematics and standing posture, respectively. Gait training focused on subject-specific changes and balance training focused on good posture with increasingly challenging stances/surfaces.

## 4.4 Results

### Clinical Metrics

Overall, the old adults had a baseline DGI score of 22.9 $\pm$ 2.5 and a follow-up score of 23.6 $\pm$ 0.9. Among the old adults, two of the sixteen had an initial score on the DGI of $\leq$ 19, with one scoring 19 and the other 15. Both subjects improved their scores a clinically significant amount (3 and 6 points, respectively) on follow-up. Both of these subjects were in the control group. Of the remaining 14 subjects, 11 scored the maximum value at baseline and the other 3 showed improvement; however, their initial scores were not low enough for that improvement to be clinically meaningful. At baseline, the active group had an average score of 23.9 $\pm$ 0.4, with seven of eight subjects receiving a perfect score. The control group had an average baseline DGI score of 21.9 $\pm$ 3.3, with four subjects receiving perfect scores. During the follow-up, the active group had an average score of 23.9 $\pm$ 0.4, with a different subject receiving a 23 than at baseline. The control group had a post-intervention score of 23.4 $\pm$ 1.2, with six subjects receiving a perfect score. These and other clinical metrics are summarized in Table 4.1.

On the sensory organization test, young adults scored 77.6 $\pm$ 6.1. Old adults had a baseline SOT score of 74.6 $\pm$ 8.5 and a follow-up score of 79.1 $\pm$ 7.4. The active group had a baseline score of 75.8 $\pm$ 9.9 and the control group scored 73.5 $\pm$ 7.5. At follow-up the active group scored an average of 79.1 $\pm$ 8.8 while the control group scored 79.1 $\pm$ 6.4. Three subjects showed improvements of greater than 8 points, with one in the active group improving by 13 points and two subjects in the control group improving by 11 and 13 points, respectively. The SOT also computes scores for how well an individual uses various sensory systems to maintain their balance, as well as a "visual preference" score that measures how much someone relies on visual information to maintain their balance even when such visual feedback is wrong. None of these individual system scores had statistically significantly different results between groups.

Table 4.1: Group mean (± standard deviation) values for DGI, SOT, TMT B, and the 3-minute walk test are summarized below.

| Metric | Group | Mean ± SD | Group Effect | Age | Stim Group | Visit |
|---|---|---|---|---|---|---|
| DGI | | score (0-24) | | | | |
| | Active Pre | 23.9 ± 0.4 | 0.097 | | 0.108 | |
| | Control Pre | 21.9 ± 3.3 | | | | |
| | Active Post | 23.9 ± 0.4 | | | NS | NS |
| | Control Post | 23.4 ± 1.2 | | | | NS |
| Composite | | score (0-100) | | | | |
| SOT | Young | 77.6 ± 6.1 | NS | | | |
| | Active Pre | 75.8 ± 9.9 | | NS | NS | |
| | Control Pre | 73.5 ± 7.5 | | NS | | |
| | Active Post | 79.1 ± 8.8 | | NS | NS | NS |
| | Control Post | 79.1 ± 6.4 | | NS | | NS |
| Trailmaking | | time (s) | | | | |
| Part B | Young | 44.8 ± 18.0 | **0.0497** | | | |
| | Active Pre | 66.9 ± 40.7 | | 0.117 | NS | |
| | Control Pre | 88.4 ± 40.3 | | **0.003** | | |
| | Active Post | 53.0 ± 19.8 | | NS | NS | NS |
| | Control Post | 68.9 ± 38.2 | | 0.072 | | NS |
| 3-Minute | | distance (m) | | | | |
| Walk Test | Young | 323.9 ± 50.1 | 0.086 | | | |
| | Active Pre | 312.6 ± 36.7 | | NS | 0.085 | |
| | Control Pre | 274.9 ± 44.4 | | **0.046** | | |
| | Active Post | 308.3 ± 28.4 | | NS | 0.157 | NS |
| | Control Post | 286.1 ± 30.1 | | 0.081 | | NS |

At baseline, young adults averaged 44.8 ± 18.0 seconds to complete TMT B, while the old adults took 78.3 ± 40.6 seconds. Old adults took significantly longer than young adults to compete the test both at baseline ($p < 0.001$) and at follow-up ($p = 0.032$). They did tend to take less time to complete the test at follow up ($p = 0.07$). The active group did not differ significantly from young adults at baseline, but the control group tended to take longer than young adults ($p = 0.058$). The active group and control groups did not differ significantly at baseline with average times-to-completion for the active group of 66.9 ± 40.7 seconds and the control group 88.4 ± 40.3 seconds ($p = 0.68$). On follow-up the groups also did not differ significantly from one another ($p = 0.88$) nor from their baseline times. The active group completed the TMT B in 53.0 ± 19.8 seconds, while the control group took 68.9 ± 38.2 seconds. One subject in the active group was dyslexic and despite several attempts, never completed the test correctly and was excluded from TMT analysis.

Table 4.2: Summary of the sensitivity of the plantar surface of subjects' feet to monofilaments calibrated to buckle at 0.07, 0.4, 2, 4, 10, and 30 grams. Subjects correctly identified whether they were being poked with a monofilament and at what location three times for the levels recorded.

| Subject | Visit | R.P1 | R.MT1 | R.MT3 | R.MT5 | L.P1 | L.MT1 | L.MT3 | L.MT5 |
|---|---|---|---|---|---|---|---|---|---|
| OF-06 | Pre | 2 | 2 | 2 | 2 | 2 | 4 | 4 | 4 |
| | Post | 0.4 | 0.4 | 2 | 0.4 | 2 | 4 | 4 | 2 |
| OF-02 | Pre | 0.07 | 0.4 | 0.4 | 0.07 | 0.07 | 0.07 | 0.4 | 0.07 |
| | Post | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| OF-10 | Pre | 0.4 | 0.4 | 0.4 | 2 | 0.4 | 0.4 | 2 | 2 |
| | Post | 0.4 | 0.4 | 2 | 0.4 | 0.4 | 0.4 | 4 | 0.07 |
| OF-05 | Pre | 2 | 10 | 4 | 4 | 2 | 10 | 4 | 10 |
| | Post | 2 | 10 | 4 | 10 | 4 | 4 | 4 | 10 |
| OF-08 | Pre | 2 | 10 | 4 | 4 | 2 | 10 | 4 | 10 |
| | Post | 0.4 | 30 | 2 | 0.4 | 2 | 10 | 4 | 4 |
| OF-12 | Pre | 2 | 2 | 2 | 2 | 4 | 2 | 2 | 2 |
| | Post | 0.4 | 0.4 | 0.4 | 2 | 2 | 0.4 | 0.4 | 2 |

All of the subjects were able to walk for the full three minutes. Two of the young adult subjects are not included in the analysis. One did not complete the test and there was a malfunction of the distance-recording equipment for the other, making the data unreliable. There was not a significant difference of group membership on distance walked, though young adults tended to walk farther than old adults (p=0.086). Given the small numbers in this study, pairwise comparisons were done in spite of the negative ANOVA. In this case, the control group of old adults walked a significantly shorter distance than young adults prior to the intervention (p=0.046) and this tended to persist following the intervention (Control vs. Young, p=0.081). The active group also tended to walk further than the control group at baseline (p=0.085).

The six subjects who completed monofilament testing appeared to have some changes in the sensitivity of the plantar side of their feet (Table 4.2). However, there were no systematic changes in the group as a whole. Six monofilaments with discreet bending forces were used and no subject saw a change of more than 2 levels before or after the intervention, with the mean change being less than one level. See Appendix C for an example of the form used.

## Quantitative Metrics

Young adults exhibited no significant changes in gait variability for any walking condition compared to normal walking (Figure 4.4). During visually perturbed walking, old adults showed an increase in SWV and SLV compared to normal walking both before and after the intervention. However, SWV and SLV during the visual trial were only significantly different from young adults before the intervention. Further, overall there was a significant decrease in SWV (40%) during the visual trial between evaluations for old adults.

Evaluated by group, the active and control groups were not significantly different from one another either before or after the intervention. Both groups had increased SWV during the visual trial compared to normal walking before (Active: 130%, Control 178%) and after (Active: 73%, Control: 99%) the intervention. Further prior to the intervention, both groups showed an increase in SLV during the visual trial compared to normal walking (Active: 145%, Control: 91%) and young adults, but only the active group's SLV remained elevated compared to normal (114% greater) at follow-up. Old adults overall and the active group walked with significantly shorter steps during the visual trial compared to normal.

In the posturography analysis, most metrics had significant differences between eyes open and eyes closed conditions within groups (Figure 4.5).

There were no significant differences within nor between groups for the 95% ellipse; however, the ANOVA suggested that eye condition (eyes open vs. eyes closed) tended to affect the area ($p = 0.067$).

In CoP path length and CoP path length per sample, the ANOVA across all groups and time periods revealed that eyes open vs. closed was a significant factor in both metrics (p's $< 0.001$). When the active and control groups were lumped together, path length was significantly affected by both group ($p = 0.032$) and group*condition ($p = 0.025$). Similarly,

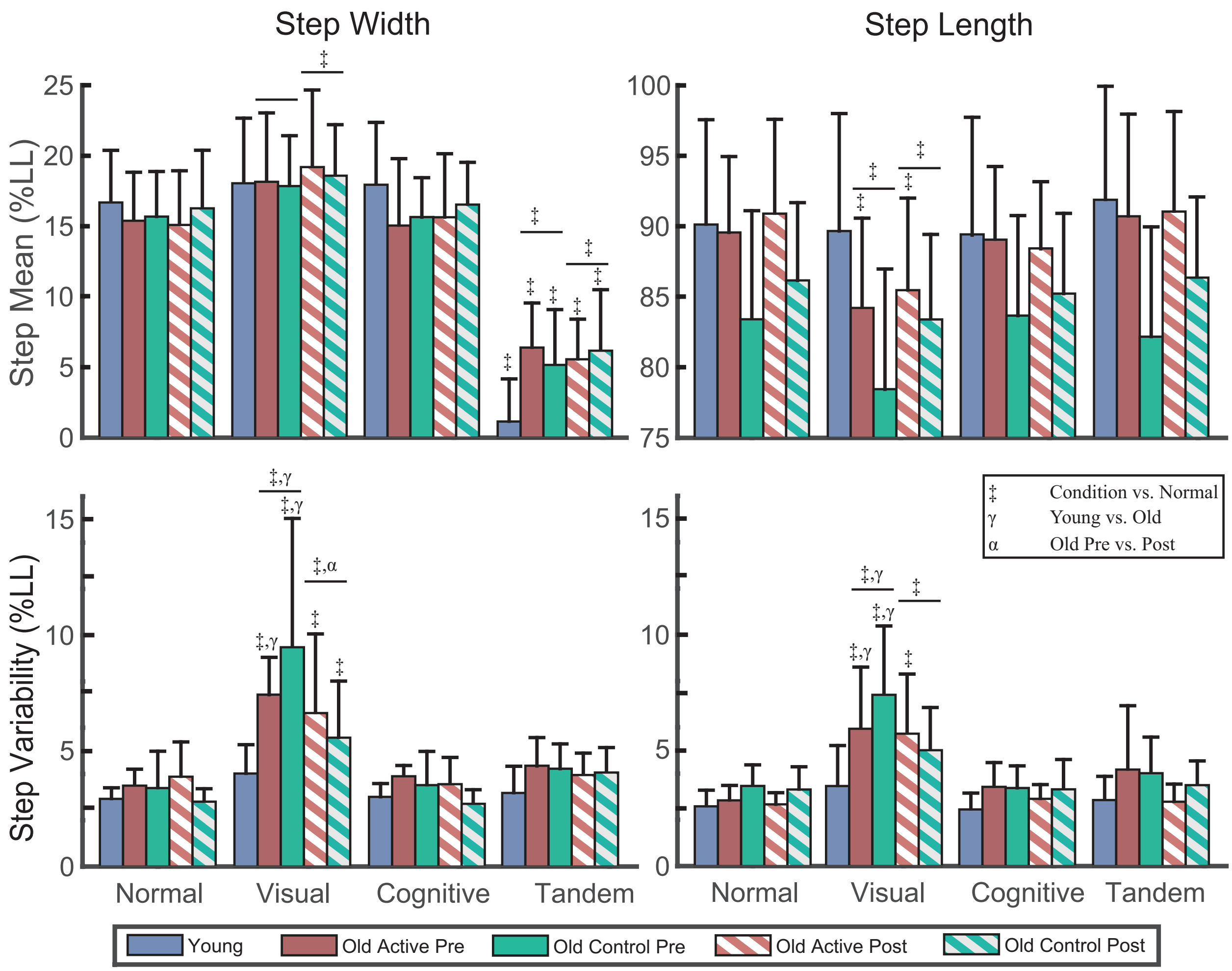



Figure 4.4: Step Width and Step Length means (SW, SL) and variability (SWV, SLV) for young adults and the active and control groups of old adults before and after the intervention. Bars over pre or post data indicate significant effects across groups. Significant differences ($p < 0.05$) are denoted: Young vs. Old ($\gamma$), Pre vs. Post ($\alpha$), Condition vs. Normal (double daggers)

group*condition significantly affected path length/sample (p = 0.048) and there was a strong trend for group (p = 0.054). More specifically, the active group was significantly different than young adults at follow-up with eyes open (p‘s < 0.001). Further, the active group also had significantly longer path length (p = 0.005) and path/sample (p = 0.004) distances than the control group at follow-up with eyes open. Total path length was significantly affected by eye condition for all groupings of subjects: young, old, active, control, pre-intervention, post-intervention. Path per sample was primarily affected by eye condition in the control group following the intervention and the combined old adults following the intervention. Several pairings within the path length and path/sample analyses were determined to be non-normally distributed. Using the Mann-Whitney U test, it was determined that for path length with eyes closed, young adults were significantly different than each of all old adults pre-intervention ($p = 0.020$), all old adults post-intervention ($p = 0.004$), the active group post-intervention ($p = 0.015$) and the control group post-intervention ($p = 0.026$). Similarly, the Mann-Whitney U test was significant for young adults vs. the lumped old adults with eyes closed post-intervention for path/sample ($p = 0.015$).

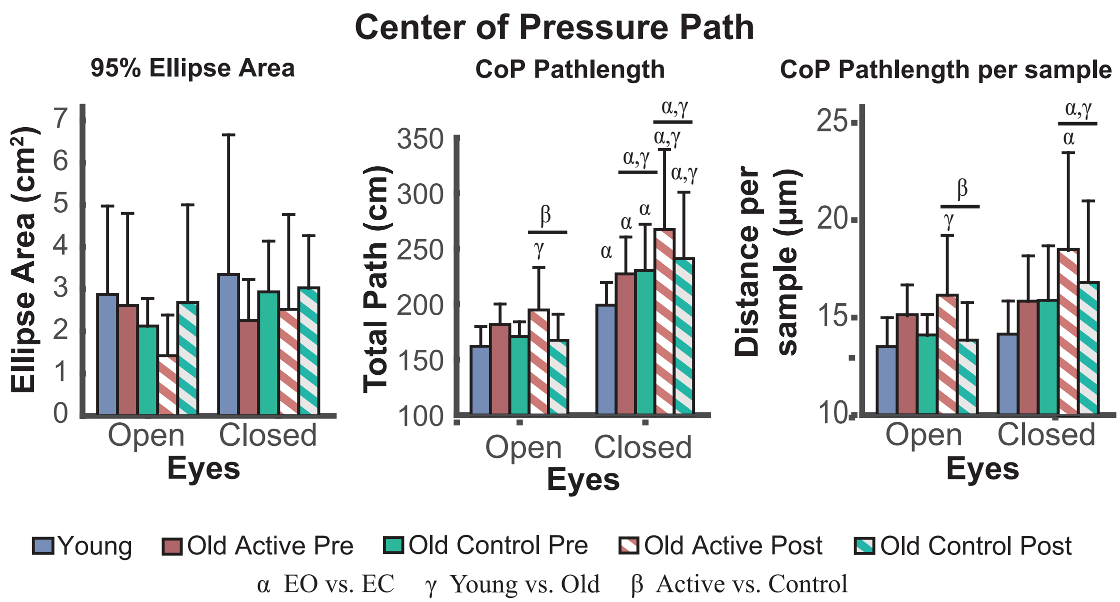



Figure 4.5: Summary of the path length and area covered by center of pressure movement when subjects had their eyes open and closed.

For CoP excursions, there were no differences between nor within groups in the medio-lateral direction (Figure 4.6). For the fore-aft direction, eye condition had a significant on the range of CoP excursion (ANOVA, p's $< 0.001$). There was only a significant effect of eye condition for the lumped old adults prior to the intervention, through depending on whether the old adults were lumped into one group or separated to active and control, the young adults may have tended toward greater fore-aft excursion with eyes closed (p's $= 0.059$, $0.155$, respectively). Similarly, for the root mean square of fore-aft excursion, eye condition had a significant effect overall (ANOVA, p's $< 0.008$), and when old adults were lumped into one group, there was a significant effect of group membership (ANOVA, $p = 0.020$). Using post-hoc testing, the lumped old adults are had significantly less fore-aft RMS excursion than young adults at both time points (p's $< 0.04$). The Kolmogorov-Smirnov test was positive for pairings of young adults vs. the lumped old adults pre-intervention and young vs. active group post-intervention. Using the Mann-Whitney U test, the lumped old adults pre-intervention and the active group post-intervention had significantly lower fore-aft RMS CoP excursion than young adults (p's = 0.013 and 0.004, respectively).

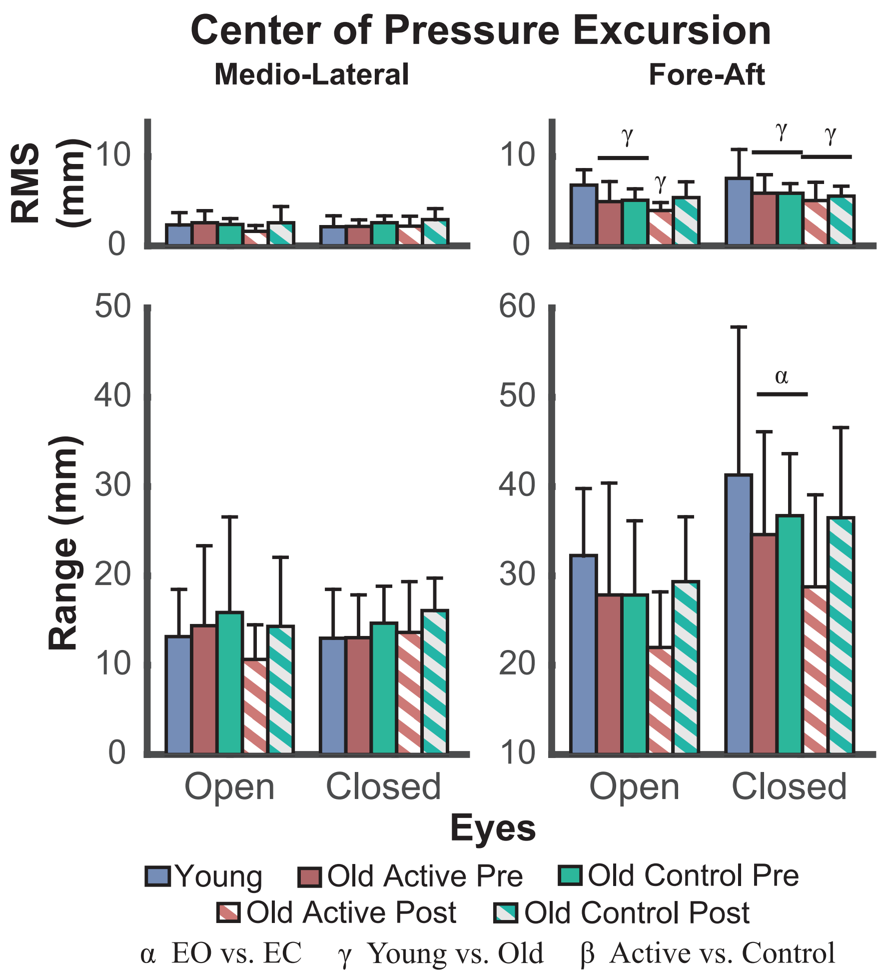



Figure 4.6: Summary of center of pressure location and range when subjects had their eyes open and closed.

For maximum medio-lateral velocity, the pairings of young adults vs. the Active group prior to the intervention with eyes both open and closed and after the intervention with eyes open were non-normally distributed, as were young vs. the lumped old adults for eyes closed prior to the intervention and eyes open at follow-up. Mann-Whitney U-tests revealed that the Active group had a significantly higher maximum medio-lateral CoP velocity than young adults for all three trials noted (p‘s $< 0.03$), while the lumped old adults did not reach significance for either trial noted (p‘s $< 0.10$). For RMS medio-lateral velocity, group membership tended to affect the outcomes when all groups and time points were considered, however it did not reach significance (ANOVA, p= 0.056). Non-parametric testing with a Mann-Whitney test showed that the active group had significantly higher RMS medio-lateral velocity at follow-up than did the control group ($p = 0.014$).

In the fore-aft direction, eye condition had a significant effect (ANOVA, p‘s $< 0.001$) on maximum CoP velocity. Group membership also tended to have an effect on maximum fore-aft velocity when the old adults were lumped together (ANOVA, $p = 0.050$). Eye condition significantly affected maximum velocity in the active group pre-intervention ($p = 0.045$) and the lumped old adults at both time points (p‘s $< 0.006$). Following the intervention, maximum velocity with eyes open and closed were no longer significantly different for the active group ($p = 0.074$). Finally, with eyes closed, old adults had greater fore-aft maximum velocity than young adults following the intervention (p =0.004), though they tended to have greater velocity prior to the intervention ($p = 0.073$).

For RMS velocity in the fore-aft direction, ANOVAs revealed that group membership (p‘s $< 0.032$) and eye condition (p‘s $< 0.001$) had significant effects. Group*Condition had a significant effect when old adults were lumped together ($p = 0.025$), but did not reach significance when all groups and time points were considered ($p = 0.085$). Post-hoc testing revealed that both active and control groups had significantly greater RMS fore-aft velocity following the intervention when their eyes were closed than when they were open. With eyes open, young adults had significantly slower velocity than both older adult groups following the intervention (p‘s $< 0.02$). Similarly, the lumped old adults had greater fore-aft RMS velocity than young adults at follow-up with eyes open ($p < 0.001$). While significance was not reached, the control group tended to have greater RMS fore-aft velocity at follow-up than the active group ($p = 0.054$). Using non-parametric tests for non-normally distributed data, young adults exhibited significantly slower RMS fore-aft velocity than old adults prior to the intervention with eyes open (Mann-Whitney, $p = 0.026$), and significantly different than both groups of old adults as well as the lumped old adults with eyes closed post-intervention (Mann-Whitney, p's $< 0.02$).

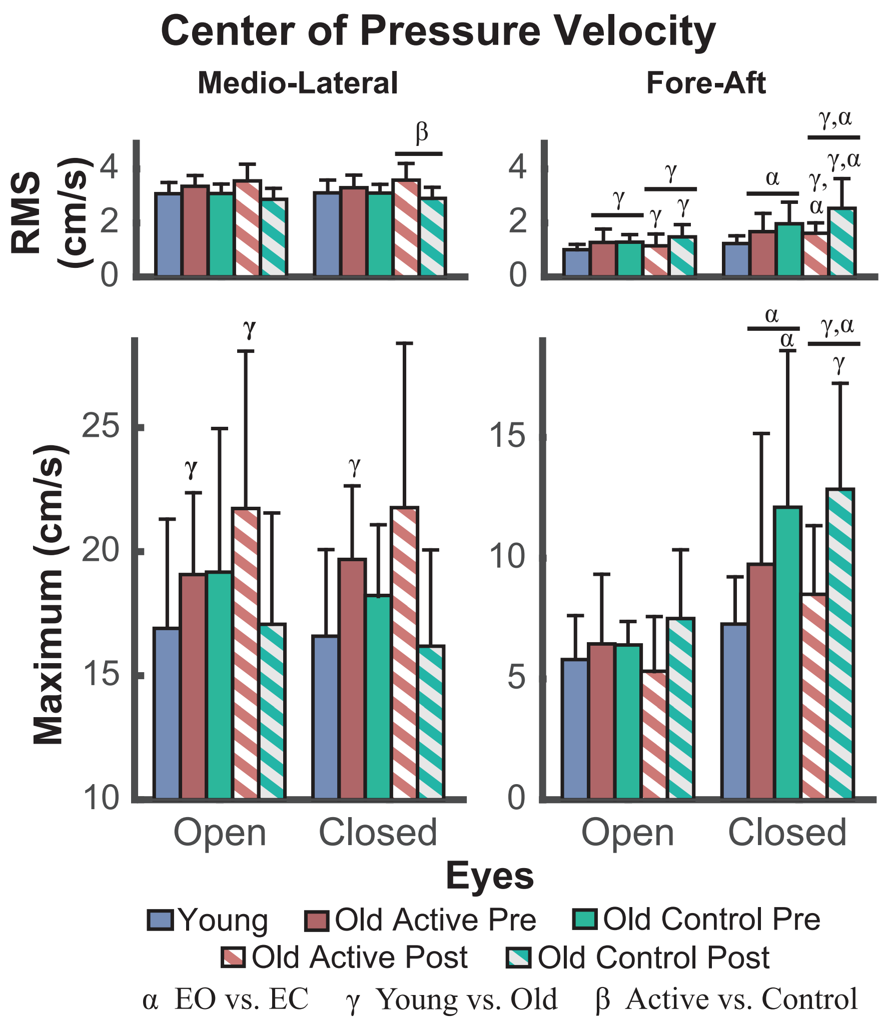



Figure 4.7: Summary of center of pressure velocity when subjects had their eyes open and closed.

Individual subjects responded to the intervention (active and control) in different ways. A number of subjects improved on various metrics, but some also showed declines on others.

These individual responses to the intervention are shown in Tables 4.3, 4.4, and 4.5. Subjects have been re-numbered in these tables to identify them as belonging to either the active or control group. Where available, minimum detectable changes (MDC) from literature are used to identify subjects with identifiable changes.

For posturography data the following values from literature were used to estimate whether subjects showed substantial changes. For the 95% ellipse area, MDCs suggested in literature range from 2.2 to 4.6 $cm^2$ with eyes open and from 3.3 to 6.5 $cm^2$ for eyes closed [86, 87]. Path length was reported by Tamburella et al. to have an MDC of 10.3 cm with eyes open and 18.6 cm with eyes closed [87]. This study used 20 cm as a marginal change and 40 cm as a substantial change. For velocity, MDC's range from 0.13 to 0.6 cm/s with eyes open and 0.2 to 1.1 cm/s with eyes closed for old adults [86, 87]. For this study, $\pm 0.25$ cm/s was considered a marginal change and $\pm 0.5$ cm/s was considered a substantial change. However, both of the studies cited used different lengths of trials which would affect MDC accuracy.

Since methods for calculating gait variability vary widely, literature values were not used to determine marginal and substantial changes. Instead, for both SWV and SLV, a 2%LL change was considered marginal and a 3+%LL change was considered substantial. Most old adults who showed some change in gait variability did so in the visual trial on step width variability or step length variability, or both. The notable exception is subject A8, whose SLV was lower in both the cognitive and narrow step width trials at follow-up.

A number of subjects showed improvement on the clinical metrics. For this study, a $\pm 20$ s change on trailmaking part B time-to-completion was considered a marginal change and a $\pm 30$ s change was considered substantial. The MDC for the DGI is 3 points, thus a 3-point change was considered marginal and any change $> \pm 3$ was considered substantial. Only two subjects started with low enough scores to improve by at least the MDC and both did. An MDC for comfortable gait speed has been suggested by Hiengkaew et al. to be 0.2 m/s [88]. The 3-minute walk test used here is a variation on the 2-minute and 6-minute walk tests, hence the cut-offs used to determine significance were estimated from MDC values from the

Table 4.3: Individual posturography metrics before and after the intervention. Subjects codes A1-A8 are active group, subject codes C1-C8 are control group. Substantial improvements are shown in dark green, marginal improvements are shown in light green, marginal declines are shown in light brown, and substantial declines are shown in dark brown. Note: subject A8 did not complete posturography at follow-up.

| | Area $cm^2$ | | | | RMS M-L Velocity $cm/s$ | | | | RMS A-P Velocity $cm/s$ | | | | Pathlength $cm$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Eyes Open | | Eyes Closed | | Eyes Open | | Eyes Closed | | Eyes Open | | Eyes Closed | | Eyes Open | | Eyes Closed | |
| Subject | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post |
| A1 | 6.08 | 3.04 | 3.77 | 6.13 | 3.21 | 3.35 | 3.18 | 3.47 | 2.30 | 2.39 | 2.60 | 5.44 | 203.4 | 211.8 | 251.5 | 388.8 |
| A2 | 2.10 | 1.09 | 1.45 | 1.48 | 3.24 | 3.81 | 2.96 | 3.73 | 1.40 | 1.91 | 1.66 | 2.06 | 180.0 | 217.7 | 209.4 | 268.7 |
| A3 | 0.91 | 0.54 | 2.75 | 0.93 | 3.31 | 3.28 | 3.19 | 3.24 | 1.10 | 1.09 | 1.14 | 1.38 | 174.4 | 173.3 | 203.1 | 214.8 |
| A4 | 5.87 | 0.72 | 1.81 | 0.94 | 2.59 | 2.78 | 2.49 | 2.79 | 1.24 | 0.81 | 1.24 | 1.09 | 143.7 | 144.2 | 168.2 | 180.9 |
| A5 | 2.75 | 1.65 | 2.76 | 5.35 | 3.82 | 3.25 | 3.80 | 3.34 | 0.77 | 1.01 | 1.05 | 1.73 | 192.1 | 169.2 | 234.7 | 228.5 |
| A6 | 0.64 | 0.58 | 0.61 | 0.90 | 3.68 | 3.67 | 3.59 | 3.75 | 0.69 | 0.92 | 1.11 | 1.83 | 180.9 | 186.2 | 222.9 | 253.5 |
| A7 | 1.03 | 2.33 | 2.71 | 1.94 | 3.76 | 4.75 | 3.94 | 4.78 | 1.26 | 1.85 | 1.88 | 2.52 | 198.5 | 260.5 | 265.3 | 334.9 |
| A8 | 1.52 | | 2.24 | | 3.25 | | 3.28 | | 1.45 | | 2.73 | | 180.6 | | 262.8 | |
| C1 | 1.42 | 2.27 | 0.90 | 3.58 | 2.82 | 2.67 | 2.83 | 2.73 | 1.14 | 1.46 | 1.34 | 2.17 | 154.0 | 155.7 | 191.7 | 215.8 |
| C2 | 3.00 | 1.05 | 1.78 | 1.41 | 2.80 | 3.18 | 2.74 | 3.00 | 1.67 | 1.05 | 1.19 | 1.77 | 167.6 | 178.1 | 180.8 | 211.0 |
| C3 | 1.34 | 0.63 | 3.98 | 2.67 | 3.45 | 3.05 | 3.42 | 3.12 | 0.83 | 0.86 | 1.24 | 2.07 | 174.3 | 158.2 | 218.2 | 227.5 |
| C4 | 2.11 | 1.76 | 2.78 | 2.14 | 3.26 | 3.25 | 3.43 | 3.17 | 1.22 | 2.03 | 3.31 | 2.91 | 174.7 | 195.4 | 292.9 | 270.9 |
| C5 | 1.55 | 1.43 | 2.88 | 2.13 | 3.08 | 2.53 | 3.10 | 2.58 | 1.08 | 1.03 | 1.49 | 1.36 | 164.4 | 137.6 | 210.0 | 178.3 |
| C6 | 2.12 | 7.66 | 2.76 | 5.37 | 2.81 | 2.16 | 2.86 | 2.28 | 1.58 | 1.60 | 2.61 | 2.75 | 179.3 | 140.4 | 262.9 | 225.0 |
| C7 | 2.53 | 4.43 | 3.80 | 3.72 | 2.79 | 2.83 | 2.89 | 2.78 | 1.32 | 1.85 | 1.88 | 2.32 | 157.9 | 173.9 | 208.4 | 223.5 |
| C8 | 2.94 | 2.19 | 4.60 | 3.23 | 3.70 | 3.33 | 3.57 | 3.62 | 1.46 | 1.97 | 2.69 | 4.97 | 195.2 | 200.3 | 277.6 | 375.6 |

Table 4.4: Individual step variability metrics before and after the intervention. Subjects codes A1-A8 are active group, subject codes C1-C8 are control group. Values that decreased by 3% Leg Length or more are shown in dark green, those that decreased between 2-3% Leg Length are shown in light green. No subject demonstrated increased in variability following the intervention.

| | Step Width Variability $\%LL$ | | | | | | | | Step Length Variaibility $\%LL$ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | | Visual | | Cognitive | | Narrow SW | | Normal | | Visual | | Cognitive | | Narrow SW | |
| Subject | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post | pre | post |
| A1 | 3.24 | 3.74 | 7.40 | 7.34 | 3.50 | 3.50 | 3.07 | 3.29 | 3.07 | 3.14 | 10.65 | 8.16 | 4.20 | 4.20 | 3.06 | 2.63 |
| A2 | 3.02 | 3.75 | 10.34 | 8.12 | 4.29 | 3.43 | 5.12 | 4.41 | 2.24 | 2.14 | 4.79 | 4.22 | 2.32 | 2.94 | 2.79 | 2.46 |
| A3 | 3.05 | 3.36 | 7.87 | 3.90 | 3.48 | 2.88 | 3.26 | 3.38 | 2.25 | 2.42 | 8.32 | 5.96 | 2.51 | 2.29 | 2.43 | 2.38 |
| A4 | 4.70 | 3.40 | 5.95 | 4.92 | 3.96 | 3.45 | 4.00 | 3.57 | 2.12 | 2.00 | 2.78 | 2.75 | 3.78 | 2.47 | 2.38 | 2.12 |
| A5 | 7.04 | 7.57 | 19.59 | 14.31 | 6.77 | 6.25 | 5.62 | 5.22 | 3.47 | 2.59 | 11.61 | 10.78 | 3.18 | 2.68 | 5.10 | 3.18 |
| A6 | 2.44 | 2.99 | 6.72 | 4.74 | 3.56 | 2.41 | 5.51 | 5.07 | 2.49 | 2.96 | 7.52 | 5.07 | 3.48 | 3.31 | 4.04 | 2.93 |
| A7 | 3.68 | 3.13 | 8.87 | 4.91 | 4.10 | 3.00 | 3.59 | 3.60 | 3.25 | 3.48 | 5.54 | 4.35 | 2.66 | 2.89 | 4.68 | 4.43 |
| A8 | 4.12 | 3.14 | 5.30 | 4.84 | 4.77 | 3.57 | 3.81 | 4.10 | 3.69 | 2.63 | 4.02 | 4.51 | 5.46 | 2.48 | 10.72 | 2.13 |
| C1 | 2.64 | 2.28 | 15.60 | 8.83 | 2.80 | 2.65 | 3.08 | 3.25 | 2.20 | 2.21 | 11.31 | 7.33 | 2.67 | 2.46 | 3.34 | 2.84 |
| C2 | 3.81 | 2.46 | 5.95 | 4.22 | 3.77 | 2.54 | 4.29 | 4.21 | 3.40 | 2.81 | 4.01 | 3.38 | 3.49 | 3.04 | 3.17 | 3.05 |
| C3 | 2.22 | 2.94 | 4.96 | 4.25 | 2.72 | 2.31 | 3.91 | 2.87 | 2.67 | 1.95 | 5.93 | 2.82 | 1.86 | 1.79 | 2.30 | 3.20 |
| C4 | 2.42 | 2.23 | 5.30 | 3.01 | 2.52 | 2.06 | 3.33 | 3.29 | 3.46 | 2.83 | 5.09 | 3.47 | 3.50 | 2.70 | 2.50 | 2.20 |
| C5 | 3.01 | 3.16 | 8.15 | 3.86 | 2.48 | 2.63 | 6.80 | 5.71 | 3.62 | 4.47 | 5.66 | 4.92 | 3.99 | 2.90 | 4.27 | 3.50 |
| C6 | 3.77 | 3.37 | 10.55 | 8.28 | 4.27 | 4.10 | 5.57 | 4.56 | 5.29 | 4.01 | 8.12 | 6.66 | 5.17 | 5.63 | 5.38 | 3.92 |
| C7 | 2.94 | 3.68 | 9.49 | 8.34 | 2.54 | 2.54 | 5.01 | 5.40 | 3.92 | 4.32 | 8.59 | 7.30 | 3.92 | 4.91 | 6.74 | 5.75 |
| C8 | 2.52 | 2.33 | 4.40 | 3.98 | 2.77 | 2.86 | 3.03 | 3.23 | 3.32 | 3.88 | 4.57 | 4.18 | 3.23 | 3.12 | 3.59 | 3.54 |

Table 4.5: Individual changes on clinical metrics before and after the intervention. Subjects codes A1-A8 are active group, subject codes C1-C8 are control group. Values in dark green are substantial improvements, values in light green are marginal improvements, values in brown represent declines.

| | TMTB $s$ | | DGI | | SOT | | Pref Speed $m/s$ | | 3minWalk $m$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject | pre | post | pre | post | pre | post | pre | post | pre | post |
| A1 | 73 | 31 | 24 | 24 | 70 | 69 | 1.20 | 1.28 | 268 | 270 |
| A2 | 48 | 71 | 24 | 24 | 74 | 78 | 1.49 | 1.42 | 326 | 323 |
| A3 | 48 | 51 | 24 | 24 | 72 | 85 | 1.22 | 1.67 | 281 | 275 |
| A4 | n/a | n/a | 24 | 24 | 87 | 88 | 1.37 | 1.26 | 343 | 342 |
| A5 | 155 | 83 | 24 | 24 | 58 | 65 | 1.23 | 1.30 | 308 | 323 |
| A6 | 44 | 51 | 24 | 23 | 86 | 87 | 1.31 | 1.24 | 382 | 339 |
| A7 | 63 | 56 | 23 | 24 | 74 | 75 | 1.03 | 1.34 | 296 | 309 |
| A8 | 37 | 28 | 24 | 24 | 85 | 86 | 1.49 | n/a | 297 | 285 |
| C1 | 85 | 76 | 22 | 24 | 58 | 71 | 1.14 | 1.29 | 286 | 317 |
| C2 | 52 | 32 | 24 | 24 | 73 | 84 | 1.33 | 1.32 | 293 | 296 |
| C3 | 136 | 127 | 24 | 24 | 81 | 88 | 1.21 | 1.47 | 311 | 314 |
| C4 | 59 | 31 | 24 | 24 | 78 | 83 | 1.29 | 1.34 | 312 | 293 |
| C5 | 135 | 77 | 24 | 24 | 68 | 70 | 1.22 | 1.14 | 253 | 252 |
| C6 | 72 | 64 | 19 | 22 | 79 | 82 | 1.27 | 0.97 | 285 | 263 |
| C7 | 131 | 116 | 15 | 21 | 77 | 76 | 1.04 | 0.83 | 175 | 239 |
| C8 | 37 | 28 | 23 | 24 | 74 | 79 | 1.21 | 1.26 | 284 | 315 |

related tests. Here a change of ±18 m was considered marginal and a change of ±29 m was considered substantial.

## 4.5 Discussion

Old adults exhibited significant improvements in gait variability after 10 consecutive days of training. However, we did not see a significant differential effect of active CN-NINM training on gait or balance in relatively healthy old adults. Gait and balance training were individualized for each subject based on gait and postural observations throughout their training sessions. Most subjects could be appropriately challenged in the balance training portion by adjusting the positions of their feet and having them stand on foam. For a few subjects, I added head-turns with eyes open - particularly if they seemed to have difficulty with head turns during walking. Most subjects were not particularly fond of the balance training portion as standing for several minutes at a time in the same position tended to fatigue their muscles. During gait training, most subjects were asked to make several changes to their gait pattern over the course of the intervention. For example, I had most subjects work on using their plantarflexor muscles to push off at the end of stance. For subjects who were able to make and maintain all adjustments deemed necessary with several days to spare, I added a few additional challenges such as turning their heads or cognitive challenges of tracking the number and colors of vehicles driving past outside (the treadmills used for training were located in a fitness center facing a window). Two subjects would not keep the PoNS device in their mouths through the whole balance or gait training session. Typically, these subjects would remove the device to swallow or comment on something or because they wanted "to take a break" from the stimulation. Usually these breaks would be less than 30 seconds, but some were longer. A few others would do this on occasion, but it was consistent and several times per session for the two subjects mentioned. Both of these subjects were randomized to the active group.

While the DGI can provide insight into fall-risk, it saturated with most of the subjects in this study. A three-point change is considered to be the minimum detectable change, and only two of our subjects started with a low enough score for a significant improvement to register on this index. Hence the DGI may not be a sensitive enough index to detect more subtle gait changes in relatively healthy old adults. That said, the subjects with low initial DGI scores ended with scores above the $\leq$19 threshold denoting increased fall risk [33]. While both were in the control group, this improvement suggests that the training approach may have been effective on its' own.

On the SOT, old and young adults did not score significantly differently at either time point. This would suggest that the old adults in this study started with fairly good standing balance. Only three of the old adults showed greater improvement than the minimum detectable change on the SOT. Thus any changes in group averages cannot be distinguished from learning effects.

Most of the old adults in the study showed a reduction in time-to-completion on the Trailmaking Part B test at follow-up with an overall average reduction of $16.9 \pm 24.6$ seconds. A previous study asked a group of adults ranging from 24-69 years of age to complete TMT B along with other cognitive tests seven times over the course of a year to evaluate the learning effects associated with repeated administration of each test [89]. At 2-3 weeks, roughly the time-frame of the present study, time-to-completion scores improved by roughly 9 seconds on average. The shortest average time was at the 3-month mark, or the 5th time subjects took the test. Subjects had an average reduction in time-to-completion of 19.5 seconds. In this study, the active group had a reduction in time to completion of $13.9 \pm 32.5$ seconds and the control group changed by $19.5 \pm 17.1$ seconds. In the present study, 10 subjects reduced their time to completion by $\geq 9$ seconds with 3 in the active group and 7 in the control group.

We did not see significant changes in the 3-minute walk test for either group. This test was included because it is straightforward to implement clinically; however, subjects in this study were healthier than individuals with which this test is typically used. Most frequently, this test is used to monitor endurance in individuals with significant gait impairments, such as due to a stroke. In the target group, therefore, individuals may not walk the entire time of the trial, negatively impacting the distance walked. In the present study, "walk as far as you can" typically translated to "walk as quickly as you feel safe" in the allotted time. As such, the results here suggest that maximum safe walking speed did not change much in the old adults in this study.

There were no systematic changes in somatosensation of the plantar surface of the foot for the six subjects tested. This lends support to the idea that any changes to gait or balance seen in this study were due to changes in either central processing of sensory information or changes in motor output, not changes in somatosensory sensitivity.

The results in SWV and SLV suggest that old adults did experience a reduction in both metrics in the visual condition following the intervention. While these differences were not significant for either the active (36% reduction) nor the control groups (44% reduction) in a pre-post comparison, the two groups did lose their significant differences from the young adult group. There were not significant differences between the two groups, thus the changes in variability when exposed to the visual perturbation were likely due either to the training regardless of the stimulation or are simply an artifact of the subjects being more familiar with the condition at the follow-up evaluation.

For several posturography metrics, old adults became less similar to young adults following the intervention. Both path length and fore-aft CoP velocity increased in old adults compared to young adults at the follow-up, particularly in the eyes closed condition. Further, following the intervention, subjects in the active group had increased path length and path length per sample with eyes open and more rapid medio-lateral RMS velocity with eyes closed compared to the control group. These results are not necessarily what we would have expected if the training were successful. However, these changes may point to old adults making a larger number of small postural adjustments at follow-up, which would be consistent with the training – particularly given that a sizable portion of the balance training was done with subjects standing on a foam pad. Further, as the fore-aft velocities increased in old adults following the intervention, subjects may have become more comfortable standing with their eyes closed over the course of the training, allowing them to make more rapid adjustments to correct their balance. At the same time, some of the significant differences in the posturography data were fairly subtle. Also interesting to note is that CoP velocity was primarily affected by vision in the fore-aft direction. Closed eyes seemed to have no effect on velocity in the mediolateral direction.

Individual subject data suggests that some subjects responded more strongly to the intervention than others. For example, A5 showed improvements across all three categories of metrics, and A3 improved on several metrics within gait variability and the clinical test categories. Similarly there were control subjects (e.g. C5 and C6) who also showed great improvements across a variety of metrics. C6 is an example of a subject who improved on a number of metrics but also showed a decrease in walking speed that was corroborated by a decreased distance walked in the 3-minute walk test. However, returning to notes on this subjects' training the loss of speed allowed the subject to improve the quality of their movement in ways that included reduced shuffling and smoother transitions of weight between limbs. While efforts were made to adjust the training exercises to be of comparable difficulty across subjects, subjects started the intervention with a wide range of differences. Several subjects exhibited Trendelenburg gait initially, while others had limb length differences that could not be corrected. There were also subjects who had very few gait abnormalities or asymmetries to work on and had to be challenged in other ways. It is possible that variations in training between subjects may have contributed to the strong response of some subjects but not others.

One inconsistency between the gait variability data and the SOT is that we found that the old adults in the study were more susceptible to inaccurate visual information than young adults in the virtual hallway, however this was not detected by a significant difference in the visual preference score on the SOT. One possible explanation is that in the virtual hallway, a set perturbation was imposed on all subjects; however in the SOT, incorrect visual feedback is a function of detected CoP motion. As a result, in the segments of the SOT with inaccurate visual information, subjects with greater fore-aft sway will end up with a substantial increase in the inaccuracy of the visual information they receive. The treadmill may have also played a role in this by reducing the somatosensory feedback subjects received while enforcing a set gait speed.

In summary, this study found that gait and balance in old adults was significantly improved following the training intervention, however there was not a differential benefit to using active CN-NINM stimulation. While substantial improvements in some traumatic brain injury subjects have been reported in non-randomized case studies within a similar or shorter time frame, the amount and intensity of training was lower in the present study. That said, with relatively healthy old adults, it would have been nearly impossible to find participants willing to participate in two or three training sessions per day. Further the old adults in this study were far healthier than the groups that have previously shown improvement with CN-NINM, thus the intervention may be more successful in a population of old adults with greater walking and balance impairment than the participants in the present study. Further work is needed to determine whether there is a subset of adults over age 65 who would benefit from gait and balance training with active CN-NINM stimulation. Given some of the changes in old adults following the intervention compared to baseline, it is possible that the training (regardless of stimulation group) had an affect on gait and balance metrics in this population. A next step to delineate learning effects vs. training effects may be to recruit a group of similar old adults to participate in two interventions with the same separation in time but no intervening training.

# Chapter 5

# Conclusions and Future Directions

Overall, the purpose of this study was to evaluate the feasibility of utilizing the Cranial Nerve Non-Invasive Neuromodulation (CN-NINM) approach to improve walking and balance in old adults at an increased risk of falling. To better evaluate gait and balance changes that clinical scales may not have the resolution or range to detect, I developed a protocol to challenge several systems that tend to decline with advancing age - specifically: sensory feedback, cognitive capacity/attention, and neuromuscular coordination - while measuring variability of step length and step width plus EMG and muscle co-activation.

Young adults were brought in for a single evaluation to provide a baseline for comparison to the old adults in the study. Old adults that passed the screening and signed consent forms came into the lab 12 consecutive days. Seventeen old adults passed the screening and agreed to participate, however one dropped out after the 5th of 12 days. Sixteen subjects completed the full 12-day study. Days 1 and 12 were dedicated to our 2-3 hour evaluation protocol. Day 1 also included device assignment. On days 2-11, subjects came in for one hour walking and balance training sessions that included a 5-10 minute warm-up with exercises focused on loosening up specific joints prior to starting the training (Figure 5.1). After the warm-up, subjects completed 20 minutes of balance training followed by 20 minutes of gait training. Most subjects spent the majority of their balance training time standing with eyes closed and no shoes with 1/3-1/2 of the time standing on a 2-inch thick foam balance pad (Figure 5.2b). Different foot positions were used to challenge subjects at an ability-appropriate level. Subjects with greater difficulty balancing spent more time with their shoes on while standing on a wooden floor, but with continued effort to improve their ability to stand in more challenging positions (feet closer together or modified tandem stance) and conditions (no shoes, foam pad, eyes closed). Most subjects completed gait training exclusively on a treadmill. Subjects were asked to make small adjustments to their gait (1 or 2 changes at a time) to improve gait symmetry and/or normalize kinematics (Figure 5.2c). Subjects worked on implementing gait changes in 5-minute increments, then they would try to maintain the changes at a faster speed or work on different adjustments for another 5-minute period.

## 5.1 Potential Factors Influencing Results of CN-NINM Training in Healthy Old Adults

Our evaluations did not reveal a significant positive effect of active CN-NINM stimulation on relatively healthy old adults. There are a number of possible explanations for this.

First, old adults with no concomitant neurological conditions may simply not be the best target group for CN-NINM intervention. The declines in neurological function and sensory feedback that come with aging may not respond to CN-NINM stimulation in the same way as something like traumatic brain injury where the neurons are mostly intact but connections need to be re-formed.

Another possibility is that 10 training sessions were too few to distinguish between active and sham CN-NINM. The rehabilitation exercises may have been novel enough compared to what subjects were doing regularly to induce the changes seen within the two-week time-frame, given that improvements were seen across both groups. Along these lines, when CN-NINM was studied for efficacy with multiple sclerosis, significant differences were not observed between active and control group subjects until the 10-week follow-up, and that

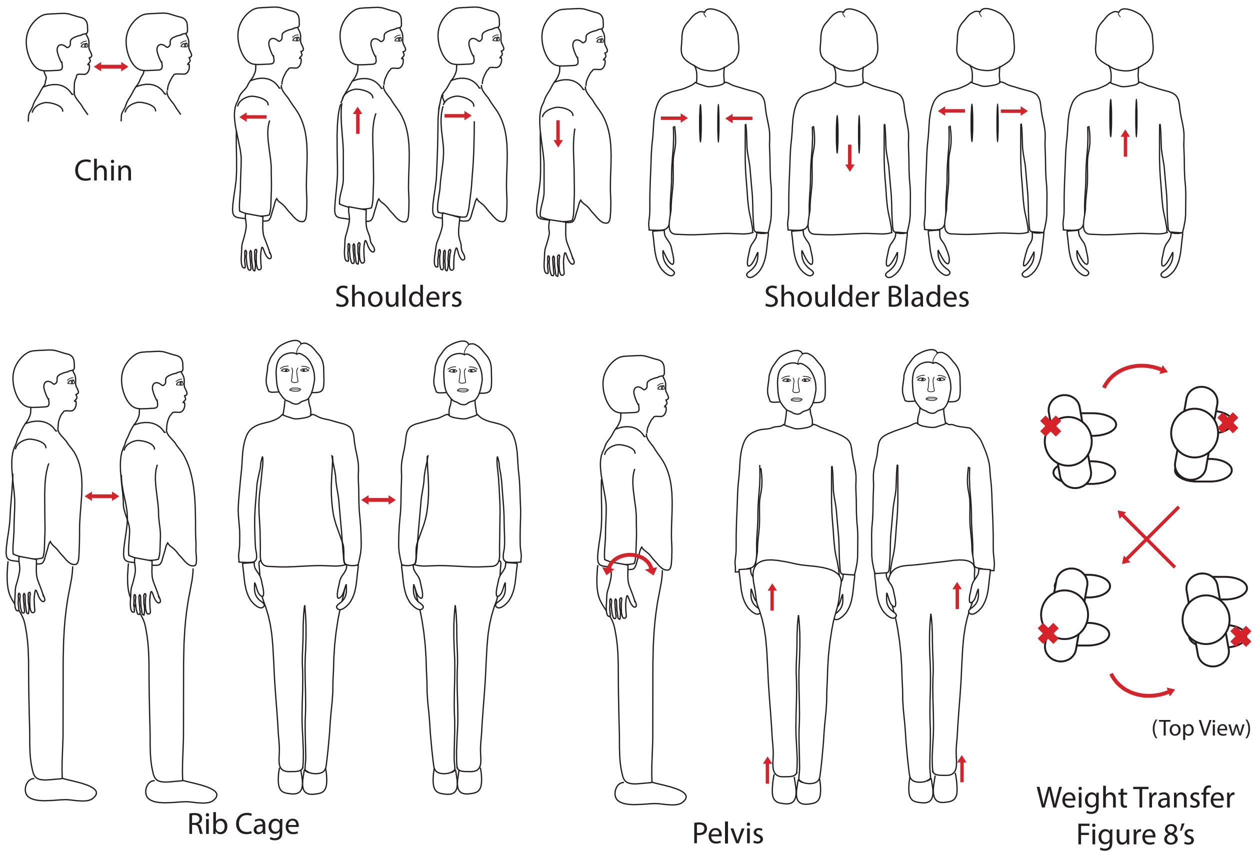



Figure 5.1: Old Adult subjects started gait and balance training sessions with movement exercises designed to isolate various joints. These included extending and retracting the chin, shoulder and shoulder blade rolls, shifting the rib cage in the anterior-posterior and medio-lateral directions, tilting the pelvis in the sagittal and frontal planes, and for some subjects working on transferring their weight in a figure-8 which mimics weight transfer in walking.

was with two training sessions per day instead of one [28].

The small numbers of a pilot study may also play a role in the outcome. With only eight subjects per group, variations between groups can have a large effect. In this case, the two subjects who started with the lowest DGI scores and were considered "true fallers" by our definition were both randomly assigned to the control group. Thus the subjects with the biggest potential for improvement did not receive active CN-NINM stimulation. In the same vein, the two subjects who were the least compliant with respect to keeping the device in their mouths through the entire training session were both in the active group. Given theories on long term potentiation, this may have thwarted any positive effects of active

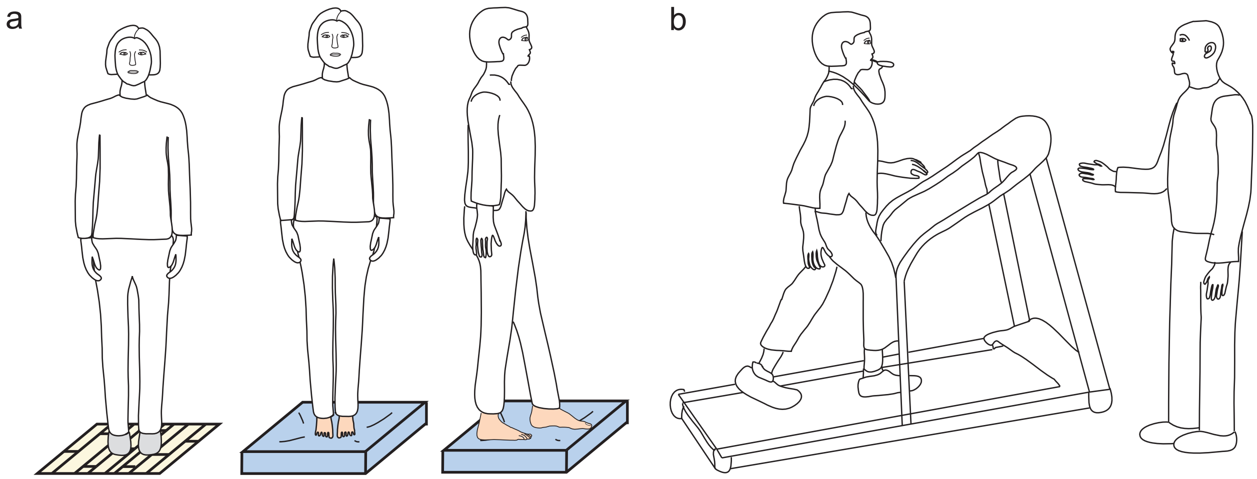



Figure 5.2: Old Adult subjects underwent ten gait and balance training sessions with active or control CN-NINM. Sessions focused on normalizing gait kinematics and standing posture, respectively. Gait training focused on subject-specific changes and balance training focused on good posture with increasingly challenging stances/surfaces.

stimulation.

Along with small numbers, for the active group, we only set the stimulation level once and day-to-day fluctuations in sensitivity were not taken into account. This was done for logistical reasons to keep me blinded to group assignments during the training phase of the study, but could have influenced the results since it is a deviation from prior work with CN-NINM. For instance, the subjects who had difficulty keeping the device in their mouth may have had the stimulation set higher than was comfortable, thus prompting their desire to "take a break" from it.

My lack of physical therapy training may have also had an effect in this study. While all subjects had the same trainer, later subjects likely received better training as I became more experienced/comfortable with the protocol. For example, there were some gait abnormalities or asymmetries that I received advice on correcting only after I had seen it in several subjects.

Another limitation with this study was that 12-consecutive days would not be viable in a clinical setting. However, for this study the timing was done to minimize the time between training sessions and evaluations while avoiding the fatigue that might be associated with asking subjects to perform a training session and an evaluation (a total of 3-4 hours) in the same day.

## 5.2 Future Directions

This research has suggested a number of opportunities for future investigation including gait and balance training in old adults and the role of vision in balance maintenance for old adults.

### Gait and Balance Training in Old Adults

It is possible that repeating a study using CN-NINM training in a different group of old adults - specifically one with a fall history and greater gait impairment than the majority of subjects in the present study - might be more successful. In order for that to happen, other exclusion criteria from the present study might need to be loosened. For instance, a number of potentially viable subjects were turned away for reasons of heart disease in accordance with guidelines for contraindication to exercise from the American College of Sports Medicine. Given that the intervention primarily involves walking, this precaution may not be necessary. Further, for much of the study, individuals with hip and knee replacements were excluded. We removed this exclusion toward the end of data collection, but not soon enough to increase the number of potential participants. Additionally, a longer intervention occurring over several weeks and limited to weekdays only might increase both participation and efficacy of CN-NINM stimulation.

It may also be worthwhile to study the effects of the training used in this study on its' own. For another iteration of this study it would be interesting to add a second control group that does not use any PoNS ®device to see if simply working with subjects to be mindful of their posture and movement patterns while working through increasingly challenging positions and speeds has a positive effect on gait and balance in old adults. If a difference were seen between control groups in the proposed setup (one with a control PoNS device, one without any device), the effect could be different from a traditional “placebo effect” in that the act of holding such a device in one’s mouth may be an unusual enough experience that it prompts/reminds subjects to focus more than they might without it.

## Role of Vision in Balance in Old Adults

The present study suggested that reliable visual feedback is particularly important for balance maintenance in old adults. In the present study, I used a virtual reality setup to manipulate subjects’ entire visual field, leading to an increase in gait variability in the older adults. Further work is needed to understand how this plays out in the real world. While in most scenarios, one’s entire visual field will not translate in the medio-lateral direction in a pseudo-random way, there are real-world situations where visual illusions are well-known to affect balance. For example, if caught between trains moving in the opposite direction, one is advised to close one’s eyes and lay down flat so that the visual disturbance does not cause one to fall into one of the moving trains. Further work is needed to understand what visual environments have an effect on balance in community-dwelling or institutionalized old adults. For example, it is possible that an environment such as a typical cafeteria with a lot of different things happening at various visual depths could be overstimulating and potentially have a destabilizing effect on older adults. Conversely, a setting that is too uniform - such as a hallway with few windows, doors, or pictures on the wall and solid décor may not provide enough visual input. If some sort of optimal range of visual environments can be identified that have a stabilizing effect on old adults, it would have implications for the design of everything from doctors’ offices to nursing homes and potentially other public buildings. Further, if such an optimal range can be identified, it may be worth seeking out a collaboration with researchers in public health who have more experience with epidemiology and quantifying the incidence of health problems.

### Gait Variability as an indicator of falls risk

While a fair bit of work has been done looking at gait variability, there is more work needed to establish standards for how variability is measured. In the literature, studies focus on various aspects of spatial and temporal metrics and use standard deviation, the coefficient of variation, and more advanced non-linear techniques to quantify the variability of gait. However, given that different research groups use different techniques, it becomes difficult to compare the outcomes of various studies. Further, most current studies linking variability to fall risk are observational in nature, reporting differences between subject groups reporting prior falls and those with no fall history. As part of establishing such a standard, it would be useful to conduct a longitudinal study that measures variability in a variety of ways with a variety of challenges and follows subjects for several years in order to prospectively link gait variability (or change therein over time) with rate of falls in a population. Such a study may also help to establish the potential effects of learning on measured variability in sequential sessions when there is no intervention. It will also be important to establish standards with an eye toward viability of translation to clinical settings, without which such standards would be futile.

## 5.3 Final Thoughts

This dissertation explored several modalities of evaluating gait and balance in old adults, as well as a novel neuromodulation intervention aimed at improving the same. While the neuromodulation did not prove more successful than control training at improving gait and balance in the present study, it may be more effective in a slightly different population or with a modified protocol. This work did contribute to understanding the importance of vision in balance maintenance among old adults, and has suggested a number of areas for further investigation of how this plays out in the real world.

# Appendix A

# Prior Work

## A.1 Pilot Subjects with Traumatic Brain Injury

The present study was motivated in part by prior work in traumatic brain injury (TBI) patients. In the late 2000's, the Tactile Communications and Neurorehabilitation Lab (TCNL) investigated the use of CN-NINM in three TBI patients. These subjects participated in a one-week CN-NINM enhanced rehabilitation protocol and underwent standardized clinical testing before and after rehabilitation. The Dynamic Gait Index (DGI) was used to assess gait abilities and a Sensory Organization Test (SOT) (NeuroCom, Clackamas, OR) was used to assess standing balance. The DGI is an 8-item inventory of progressively challenging gait tasks (e.g. walk and turn your head, change speeds, navigate stairs) with a maximum score of 24. Studies have shown that scores below 19 indicate a higher risk of falls [33]. Initially all 3 subjects scored below a 10, with one subject unable to complete the task. Following training, all subjects improved to >22 (Fig. A.1a). The SOT is a widely used quantitative clinical balance test which uses computerized dynamic posturography to evaluate the integration of visual, vestibular and proprioceptive inputs on a scale of 0-100. It has well documented age-related norms. Following CN-NINM rehabilitation, all TBI patients showed improvements in balance of >20 points on the SOT.

In addition to these metrics, I performed quantitative gait analysis and electromyography (EMG) on the third subject before and after the intervention. Following training, the subject showed an 88% increase in gait speed, a 60% increase in stride length, a 46% increase in cadence, and a 31% reduction in step width. Prior to training, the timing of the subject's left soleus and vastus lateralis were active at abnormal times during gait (shaded areas in Fig A.1b). After CN-NINM rehabilitation, these muscles were active (line traces in Fig A.1b) at times more typical of healthy individuals (dark black bars below traces in Fig 2b) [60].

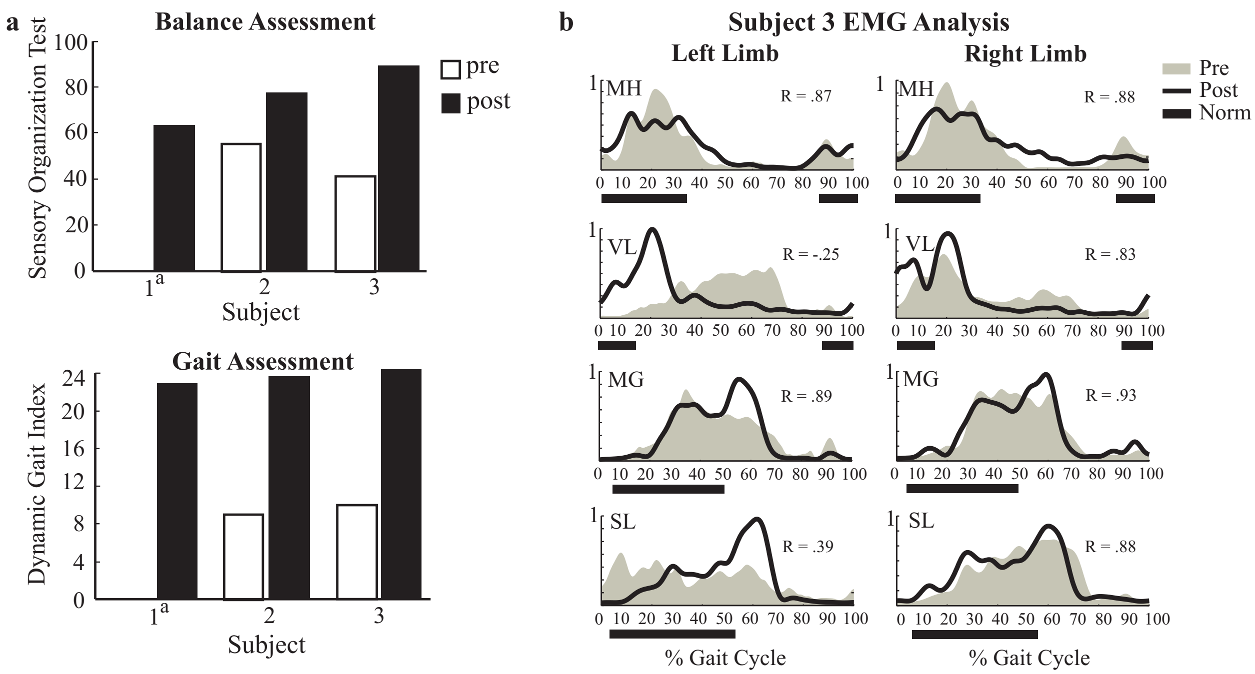



Figure A.1: 3a. Dynamic Gait Index scores for three patients with chronic traumatic brain injury before and after a 5-day intervention using CN-NINM. 3b. Muscle activation traces for one TBI subject before and after CN-NINM intervention with normal timing for muscles.

## A.2 Healthy Adults Pilot Study

Given the dramatic changes in gait and balance of individuals with neurological disorders, I wanted to test whether gait training with CN-NINM could induce changes in the gait of healthy adults. This was of particular interest because the implication of modifying gait in both healthy individuals as well as severely affected patients with neurological disorders would be that patients with mild impairments or functional declines that were not clinically detectable could benefit from this intervention. For this study, step width variability was selected as the outcome measure because it is less susceptible than clinical measures to ceiling effects. The subjects in this study would have likely all scored perfectly on most clinical gait metrics.

Five healthy young and middle-aged adults were recruited to participate in two weeks of gait training with and without the PoNS device. Subjects walked 30-minutes per day for five days during each training week and step width variability was analyzed at the beginning and end of each week. I included a washout period of at least three weeks between test weeks, and the order of the CN-NINM and control weeks was randomized. Gait tests were conducted using an active motion capture system with markers on the heels of subjects' shoes as they walked on a treadmill facing away from the 3-camera system. Step width was defined as the perpendicular distance between the heel of one foot and the line of progression of the contralateral foot [19, 90]. Step width variability was calculated as the standard deviation of step width over at least 300 strides. Subjects also walked under single- and dual- task conditions, (while performing serial three subtractions [91]). Subjects showed no change in step width variability during the control week, but all subjects had a significant decrease in step width variability for the dual task ($p < 0.005$) condition and a trend toward decreased step width variability for the single task condition ($p = 0.06$) following training with CN-NINM (Fig. A.2).

These pilot results were extremely encouraging because they represented the first demonstration that CN-NINM could affect gait performance in a population without neurological disorders or injuries. Step width variability is considered indicative of medio-lateral balance, which is inherently unstable during gait [39, 92, 93]. Sensorimotor control of medio-lateral foot placement is required to maintain balance in this direction[39, 93]. The reduced step width variability demonstrated here may represent an improvement in medio-lateral stability and a reduction in the need for lateral balance correction. This dissertation sought to assess

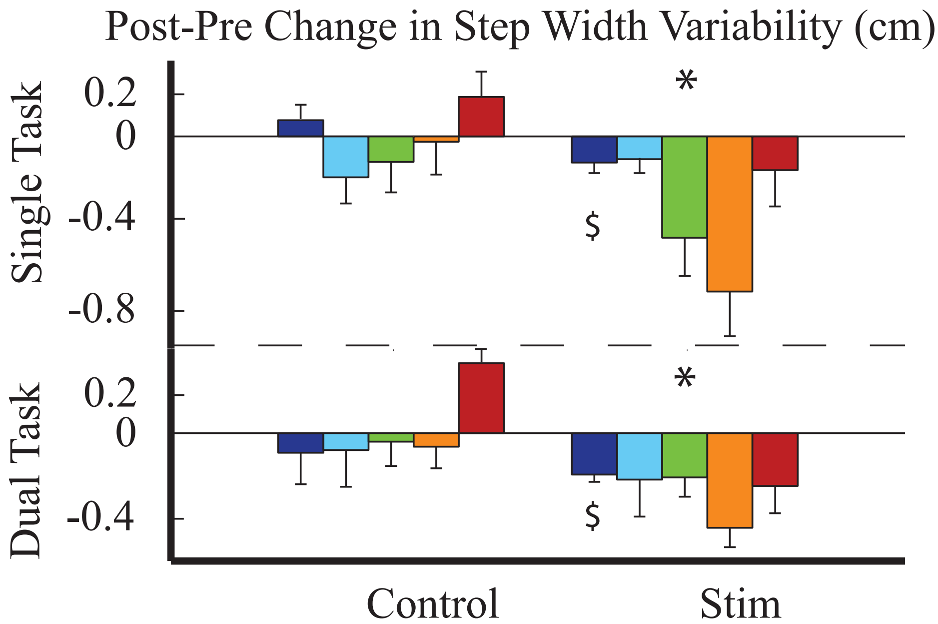



Figure A.2: Change in Step Width Variability for five healthy adults recruited to perform 30 minutes of walking on five consecutive days with and without CN-NINM.

whether such improvements could be achieved in old adults at risk for falls.

# Appendix B

# Additional Metrics

In addition to the pre-post metrics reported in Chapter 4, we also collected EMG data before and after the intervention in old adults in line with Aim 3: to investigate the sensorimotor mechanisms underlying the effect of CN-NINM enhanced training. The purpose of this portion of the study was to investigate whether the effects of CN-NINM on gait could be partially explained by changes in sensorimotor function, as measured by muscle activity.

## B.1 EMG Methods

Sixteen old adults (70.7 $\pm$ 4.5 years, 1.65 $\pm$ 0.05 m, 69.7 $\pm$ 11.1 kg, 15 female) participated in the study and were randomized to complete 10 sessions of walking and balance training while utilizing either active or control (sub-sensory threshold) CN-NINM stimulation. The evaluation methods are the same as chapter 3. Briefly, subjects walked in a virtual hallway back-projected on a semi-circular screen surrounding the front of the treadmill with three conditions: normal walking, walking with incongruent visual information and dual-task walking. Motion capture and electromyography (EMG) data were collected synchronously. EMG was collected bilaterally from the semitendonosis (MH), vastus lateralis (VL), medial gastrocnemius (MG), soleus (SL), and tibialis anterior (TA) muscles. Kinematic data was used to delineate gait cycles.

EMG data was band-pass (1-350 Hz) filtered to remove noise and drift, then rectified and low-pass filtered at 10 Hz to obtain the muscle activation envelope. The envelope was then normalized to the RMS average of the normal trial. Using the kinematic data, EMG data was split into gait cycles and interpolated to 1000 points per gait cycle then ensemble averaged for each subject. The muscle activation traces were compared across groups and conditions at five intervals [51]: loading response (0-10%), mid-stance(10-30%),terminal stance/pre-swing (30-60%), initial swing (60-73%), and terminal swing (87-100%). We computed co-activation indices two ways – as the area of overlap between two muscles and as the normalized area of overlap per Winter's definition [75] (Figure B.1), for muscle pairs Medial Hamstring-Vastus Lateralis (MH-VL), Medial Gastrocnemius-Tibialis Anterior (MG-TA), and Soleus-Tibialis Anterior (SL-TA).

EMG data was unavailable for one older adult at the follow-up due to equipment malfunction, thus for old adults, 16 subjects are evaluated prior to the intervention and 15 at follow-up.

## B.2 EMG Results

At baseline, the active and control groups did not differ significantly from one another in muscle activation patterns, however, there were some differences between the groups in other comparisons (Figure B.2). For example, the active group had elevated MH activity in the visual condition compared to both normal walking and young adults in four of the five gait cycle segments, while the control group had an increase compared to normal walking in one of the five segments, but did not differ significantly from normal walking. In fact, there were only two comparisons that showed similarity between groups at baseline. Both groups had increased MH activity compared to young adults during the visual trial in terminal stance/pre-swing. They also both showed an increase in VL activity in the visual trial compared to normal walking during mid-stance.

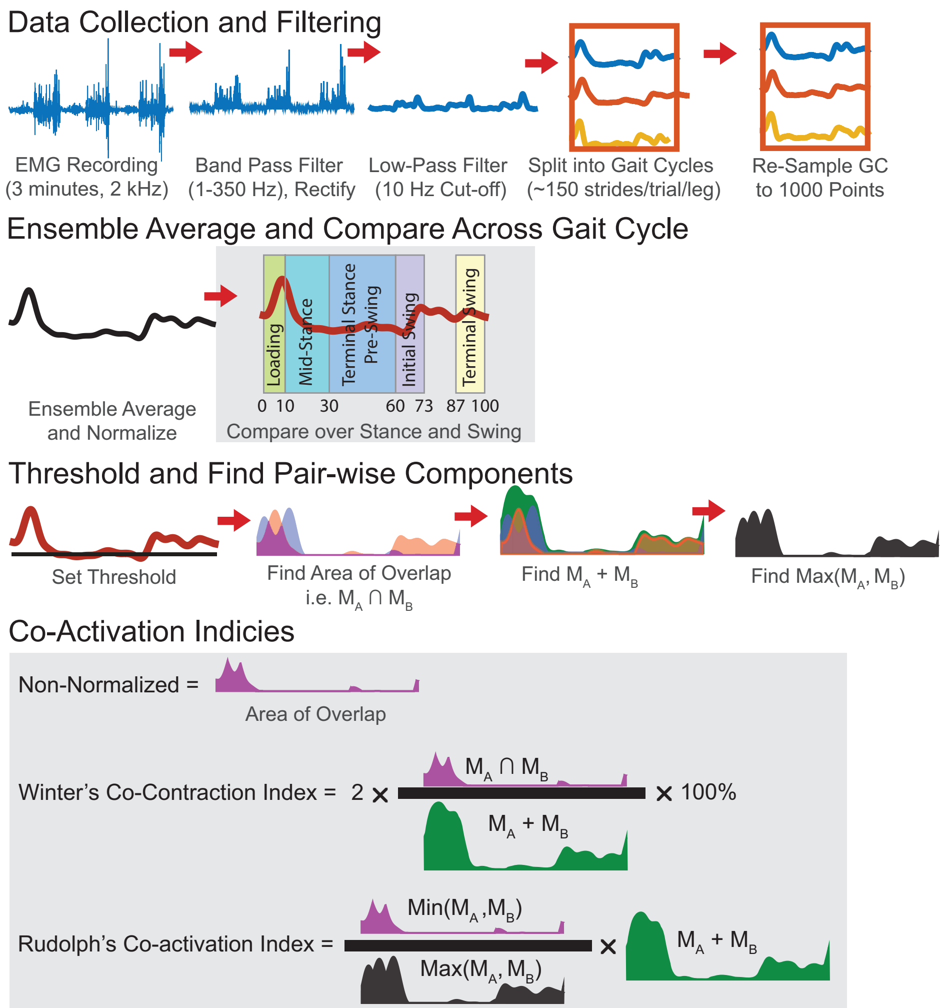



Figure B.1: Visual description of how EMG data was processed for each type of comparison: ensemble average group traces and various co-activation indicies.

Following the intervention, there was one significant difference between groups: MG activation in the dual-task trial was significantly higher during loading response in the active group compared to the control group. Also in the active group, VL activity was significantly different during initial swing between visits. In the control group, VL activity was significantly different between visits during terminal stance/pre-swing in normal walking. There were also similarities in VL activation between groups. During terminal stance/pre-swing and initial swing, both groups of old adults had increases in VL activity in the visual and dual-task conditions compared to young adults.

Both groups of old adults had increased MH-VL and SL-TA co-activation in the visual

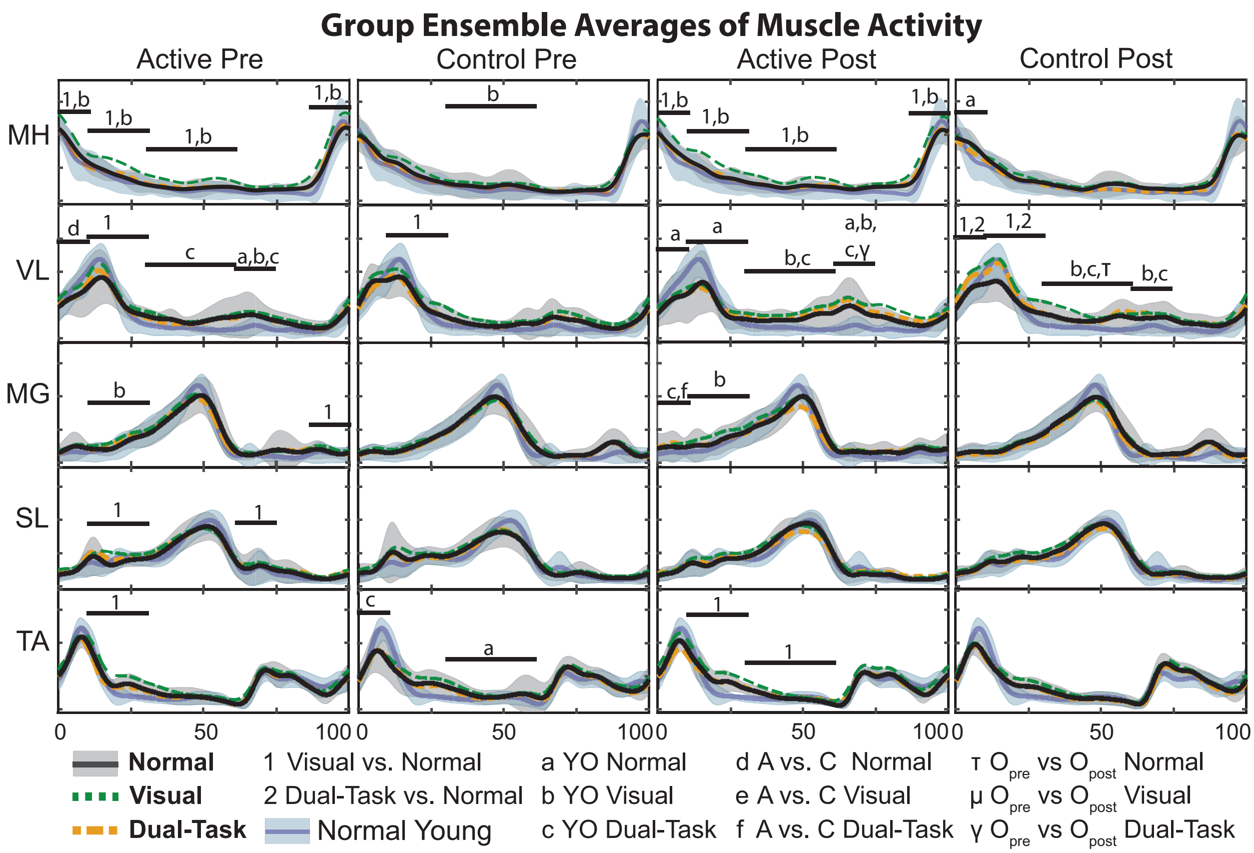



Figure B.2: Electromyography traces for old adults in the active and control groups before and after the intervention. The mean ± standard deviation is shown in black with gray shading for each group. EMG traces for the visual and dual-task trials are shown with green and yellow dashed lines, respectively. Young adults are shown for comparison in blue with shading. Symbols denoting significant difference between groups, sessions, and conditions are noted on the figure.

trial compared to normal walking using the non-normalized and Rudolph formulas both before and after the intervention. There were no significant differences between active and control groups at either time point, nor were there significant differences within each group between time points. The combined groups had significantly greater SL-TA co-activation in the visual trial compared to young adults using the non-normalized and Rudolph formulas prior to the intervention. SL-TA co-activation was also greater than young adults in the individual groups using the Rudolph formula. These differences from young adults disappeared following the intervention. Prior to the intervention, normal SL-TA co-activation was higher for both groups compared to young adults using the non-normalized formula, and in the control group compared to young adults using Winter's formula. The active group also tended to have higher SL-TA co-activation using Winter's formula in normal walking, but it did not reach significance (p = 0.0589). Using the non-normalized formula the combined old adult groups had greater MG-TA co-activation compared to young adults prior to the intervention in the visual trial, and the active group had significantly greater MG-TA co-activation in the visual trial following the intervention. The active group's MG-TA co-activation following the intervention was also increased compared to normal, though not significantly (p = 0.069). Prior to the intervention, the combined old adult groups also showed non-significant increases in MG-TA co-activation compared to normal walking (p = 0.053) and young adults (p = 0.086), using the Rudolph formulation.

## B.3 Discussion

The training for a number of subjects included a focus on picking up one's feet and using the plantarflexors to push-off during terminal stance. Given this, I would have expected to potentially see more changes in MG, SL, and TA activation following the intervention. Though changes in TA activation might be more expected in mid-swing, which we did not include in this analysis. Interestingly, SL-TA co-activation appears to have decreased in old adults compared to young following the intervention in both the normal and visual trials, an observation not apparent from the EMG traces. Subtle changes in motor control timing may have contributed to this difference.

It does seem like old adults responded to the challenging conditions more with proximal segment muscles rather than more distal muscles. This is consistent with known age-related changes in muscle control that suggest old adults tend to use hip strategies for maintaining their balance rather than ankle strategies [51]. This evident in both the group averages of EMG traces and MH-VL co-activation.

Given that there were not a substantial number of significant differences between groups,

Table B.1: Group mean (± standard deviation) values for Normal, Visual and Dual-Task Conditions for all three formulations of the co-activation index and 3 muscle pairs. Group and condition main effects or interactions from a repeated measures ANOVA are reported.

| Metric | Group | Normal | Visual | Dual-Task | p Group | p Condition | p Group × Condition |
|---|---|---|---|---|---|---|---|
| Non-Normalized | | | | | | | |
| MH-VL | Young | 21.4 (10.1) | 27.9 (10.8) | 27.9 (10.8) | NS | <**0.001** | 0.081 |
| | ActPre | 17.8 (8.8) | 38.4 (14.3) | 19.1 (11.1) | | | |
| | ConPre | 24.2 (6.8) | 44.9 (24.5) | 21.9 (8.4) | | | |
| | ActPost | 16.0 (9.2) | 37.0 (13.9) | 20.8 (14.4) | | | |
| | ConPost | 21.8 (8.5) | 37.9 (19.2) | 20.9 (8.7) | | | |
| MG-TA | Young | 9.3 (5.9) | 12.8 (12.8) | 10.7 (5.9) | **0.004** | <**0.001** | NS |
| | ActPre | 15.8 (6.3) | 24.0 (7.7) | 15.9 (4.9) | | | |
| | ConPre | 15.6 (3.1) | 21.7 (8.3) | 13.3 (2.8) | | | |
| | ActPost | 16.4 (4.3) | 26.3 (8.0) | 19.4 (8.3) | | | |
| | ConPost | 14.2 (3.7) | 17.7 (5.9) | 11.7 (5.4) | | | |
| SL-TA | Young | 12.9 (5.4) | 16.4 (13.5) | 14.8 (6.2) | NS | <**0.001** | NS |
| | ActPre | 19.4 (6.5) | 31.6 (15.7) | 20.5 (9.4) | | | |
| | ConPre | 19.4 (10.5) | 28.6 (12.7) | 18.7 (10.7) | | | |
| | ActPost | 16.9 (6.3) | 26.6 (9.9) | 22.3 (11.1) | | | |
| | ConPost | 15.6 (5.6) | 22.6 (10.8) | 14.6 (8.1) | | | |
| Winter's Formulation | | | | | | | |
| MH-VL | Young | 48.8 (15.7) | 55.3 (15.4) | 47.5 (13.6) | NS | <**0.001** | NS |
| | ActPre | 42.7 (16.2) | 53.5 (12.3) | 42.3 (18.7) | | | |
| | ConPre | 53.7 (12.3) | 62.6 (14.0) | 49.9 (14.5) | | | |
| | ActPost | 40.7 (19.9) | 51.8 (17.4) | 45.8 (26.0) | | | |
| | ConPost | 50.4 (13.3) | 56.7 (14.7) | 45.2 (16.0) | | | |
| MG-TA | Young | 18.2 (11.0) | 24.5 (22.7) | 19.4 (10.5) | **0.012** | **0.003** | NS |
| | ActPre | 30.2 (10.9) | 37.6 ( 9.2) | 31.2 (8.6) | | | |
| | ConPre | 29.7 (6.0) | 35.7 (9.2) | 26.9 (5.9) | | | |
| | ActPost | 31.2 (8.8) | 39.3 (8.5) | 39.0 (20.7) | | | |
| | ConPost | 27.2 (8.3) | 30.7 (8.8) | 23.7 (9.1) | | | |
| SL-TA | Young | 25.3 (10.8) | 30.3 (23.0) | 26.3 (11.1) | NS | <**0.001** | NS |
| | ActPre | 36.4 (13.1) | 46.3 (15.1) | 36.2 (10.1) | | | |
| | ConPre | 36.8 (20.7) | 45.1 (18.5) | 35.9 (19.9) | | | |
| | ActPost | 30.8 (10.9) | 38.9 (8.2) | 42.2 (23.7) | | | |
| | ConPost | 28.9 (10.0) | 35.2 (11.6) | 28.2 (13.6) | | | |
| Rudolph's Formulation | | | | | | | |
| MH-VL | Young | 30.0 (17.8) | 40.6 (21.7) | 27.3 (11.4) | NS | <**0.001** | NS |
| | ActPre | 23.7 (13.1) | 54.0 (24.1) | 25.9 (16.9) | | | |
| | ConPre | 33.9 (12.5) | 68.7 (42.3) | 30.4 (13.9) | | | |
| | ActPost | 21.5 (14.7) | 52.3 (24.4) | 29.7 (22.0) | | | |
| | ConPost | 30.1 (13.7) | 54.2 (27.5) | 27.9 (12.7) | | | |
| MG-TA | Young | 10.6 (7.2) | 17.4 (23.7) | 12.2 (7.1) | **0.004** | <**0.001** | NS |
| | ActPre | 19.2 (9.3) | 30.1 (11.0) | 19.1 (7.3) | | | |
| | ConPre | 18.4 (4.2) | 26.9 (11.9) | 15.5 (3.7) | | | |
| | ActPost | 19.7 (6.1) | 33.1 (11.0) | 26.0 (16.9) | | | |
| | ConPost | 16.7 (5.1) | 21.2 (8.1) | 13.5 (7.0) | | | |
| SL-TA | Young | 15.2 (7.2) | 22.5 (26.8) | 17.4 (8.1) | NS | <**0.001** | NS |
| | ActPre | 24.5 ( 11.2) | 43.6 (29.1) | 25.8 (14.1) | | | |
| | ConPre | 25.7 (17.1) | 39.2 (21.7) | 21.5 (16.9) | | | |
| | ActPost | 20.4 (9.1) | 33.6 (14.0) | 31.4 (24.6) | | | |
| | ConPost | 18.6 (7.7) | 28.3 (15.5) | 17.8 (11.0) | | | |

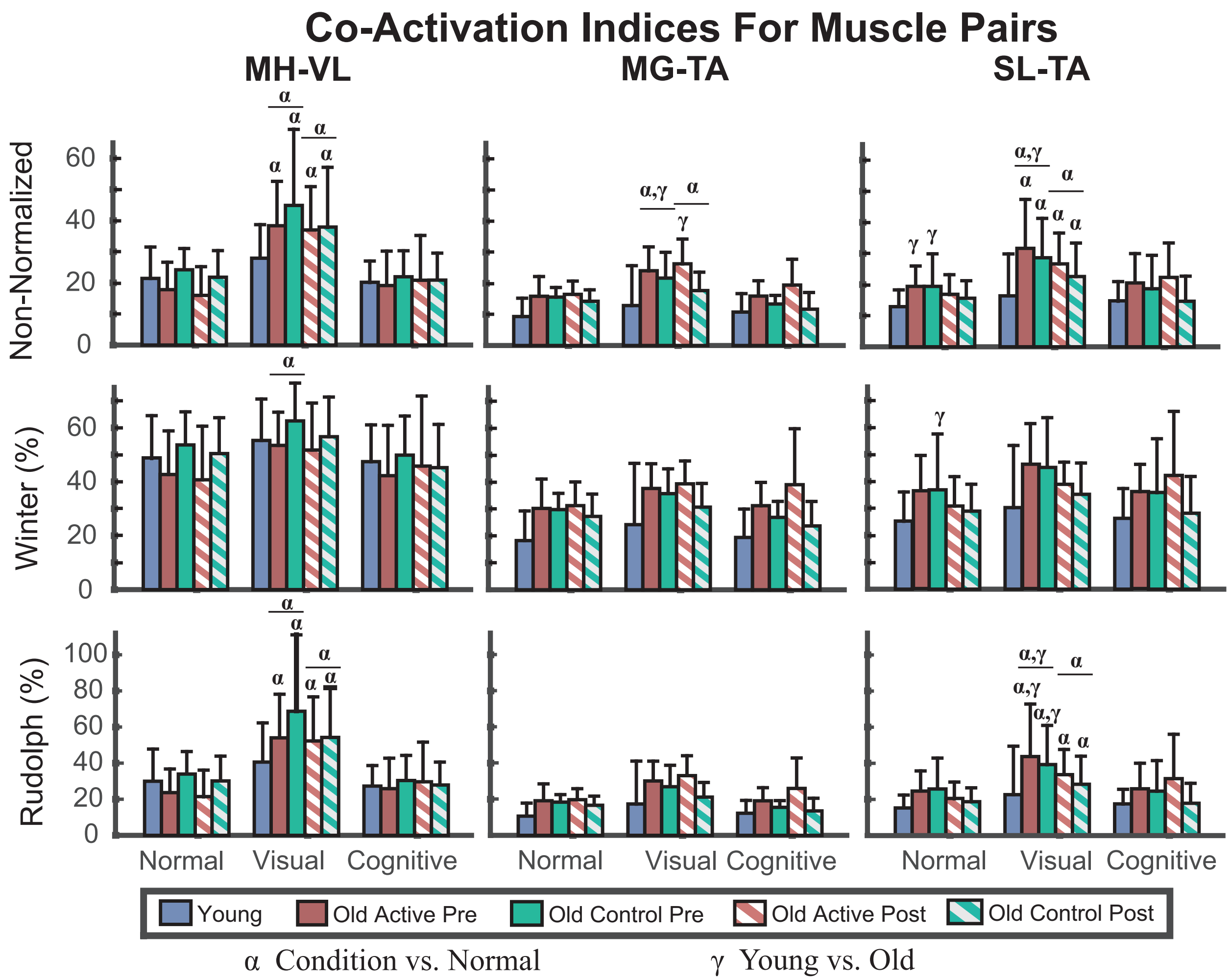



Figure B.3: Muscle co-activation before and after the intervention using three formulations. Significant differences ($p<0.05$) are denoted, there were no significant differences Pre-Post intervention or between active and control groups.

it is difficult to know whether changes in muscle activation and co-activation following the intervention are due to the training portion of the intervention or a learning effect. There could also be differences as a result of different placement of EMG sensors, however it is unlikely that this would result in any systematic changes.

# Appendix C

# Data Collection Forms

This appendix includes the forms used during data collections. They include:

**General Data collection sheet:** Summary of demographic, test scores, and order of quantitative tests. This form changed a bit with changes in the study - early versions did not include the Falls Efficay nor vision testing blanks.

**Dynamic Gait Index**: 3rd party form, includes script and scoring for eight items tested. This test was scored by a physical therapist.

**Trailmaking Part B:** 3rd party form, standard layout for TMT B. Instructions were given on a smaller version with only 1 to D, then subjects were timed completing this form.

**Tinneti Falls Efficacy Scale:** 3rd party form, subjects filled out on their own with special instruction given to note that in this case a "1" meant they were very confident that they could perform the task without falling and "10" meaning they were fairly certain they could not perform the task without falling.

**Semmes-Weinstein Monofilament:** Form I developed to record sensitivity at locations shown.

# Gait and Balance Evaluations

Subject ____________________ Baseline Follow-up Date ________________

## Anthropomorphic Data

| | | | | | |
|---|---|---|---|---|---|
| Height | ________ in | Weight | ________ lb | Age | ________ y |
| | | | | Gender | ________ |

## Clinical Assessments

| | | | | | | |
|---|---|---|---|---|---|---|
| Trailmaking B Time | ________ s | DGI Score | ________ /24 | Vision: | both eyes | 20/ ________ |
| | | | | | R. eye | 20/ ________ |
| SOT Composite Score | ________ /100 | Falls Efficacy | ________ /100 | | L. eye | 20/ ________ |
| Time to walk 20ft | ________ s | Preferred Walking speed | ________ ft/s | ________ m/s | | |

Semmes Weinstein

| | R.P1 | R.MT1 | R.MT3 | R.MT5 | | L.P1 | L.MT1 | L.MT3 | L.MT5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| min detected | ----------- | ----------- | ----------- | ----------- | g | ----------- | ----------- | ----------- | ----------- | g |

## Quantitative Tests

Order of Postural Sway

Eyes Open ________
Eyes Closed ________

Overground Walking
__________ laps + ____________ ft

3-minute walk test ________ ft

Order of Treadmill Walking Tests

Plain VR hallway ________
Perturbed VR Hallway ________
Cognitive Task ________
Walk on a line ________

## EMG Channels

| | | | |
|---|---|---|---|
| L. MGAS | ________ | R. MGAS | ________ |
| L. SOL | ________ | R. SOL | ________ |
| L. MHam | ________ | R. MHam | ________ |
| L. TA | ________ | R. TA | ________ |
| L. VL | ________ | R. VL | ________ |

**DYNAMIC GAIT INDEX** **DATE: _____________**

Grading: record the lowest category that applies.

**1. Gait level surface**: <u>*Instructions:*</u> *Walk at your normal speed from here to the next mark (20').*
(3) Normal: walks 20', no assistive devices, good speed, no evidence for imbalance, normal gait pattern.
(2) Mild impairment: walks 20', uses assistive devices, slower speed, mild gait deviations.
(1) Moderate impairment: walks 20', slow speed, abnormal gait patters, evidence for imbalance.
(0) Severe impairment: cannot walk 20' without assistance, severe gait deviations or imbalance.

**2. Change in gait speed.** <u>*Instructions:*</u> *Begin walking at your normal pace (for 5'), when I tell you "go", walk as fast as you can (for 5'). When I tell you "slow", walk as slowly as you can (for 5').*
(3) Normal: Able to smoothly change walking speed without loss of balance or gait deviation. Shows significant difference in walking speeds between normal, fast and slow paces.
(2) Mild impairment: Is able to change speed but demonstrates mild gait deviations, or no gait deviations but unable to achieve a significant change in velocity, or uses as assistive device.
(1) Moderate impairment: Makes only minor adjustments to walking speed, or accomplishes a change in speed with significant gait deviations, or changes speed but loses balance but is able to recover and continue walking.
(0) Severe impairment: Cannot change speeds, or loss balance and has to reach for a wall or be caught.

**3. Gait with horizontal head turns.** <u>*Instructions:*</u> *Begin walking at your normal pace. When I tell you to "look right", keep walking straight, but turn your head to the right. Keep looking to the right until I tell you "look left", then keep walking straight and turn your head to the left. Keep your head to the left until I tell you, "look straight", then keep walking straight, but return your head to the centre.*
(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild impairment: Performs head turns smoothly with slight change in gait velocity, i.e. minor disruption to smooth gait path or uses walking aid.
(1) Moderate impairment: Performs head turns with moderate change in gait velocity, slows down, staggers, but recovers, can continue to walk.
(0) Severe impairment: Performs task with severe disruption of gait, i.e. staggers outside 15" path, loses balance, stops, reaches for wall.

**4. Gait with vertical head turns.** <u>*Instructions:*</u> *Begin walking at your normal pace. When I tell you to "look up", keep walking straight, but tip your head and look up. Keep looking up until I tell you, "look down". Then keep walking straight and turn your head down. Keep looking down until I tell you, " look straight", then keep walking straight, but return your head to the centre.*
(3) Normal: Performs head turns smoothly with no change in gait.
(2) Mild impairment: Performs head turns smoothly with slight change in gait velocity, i.e. minor disruption to smooth gait path or uses walking aid.
(1) Moderate impairment: Performs head turns with moderate change in gait velocity, slows down, staggers, but recovers, can continue to walk.
(0) Severe impairment: Performs task with severe disruption of gait, i.e. staggers outside 15" path, loses balance, stops, reaches for wall.

**5. Gait and pivot turn.** *<u>Instructions:</u> Begin walking at your normal pace. When I tell you, "turn and stop", turn as quickly as you can to face the opposite direction and stop.*
(3) Normal: Pivot turns safely within 3 seconds and stops quickly with no loss of balance.
(2) Mild impairment: pivot turns safely in >3 seconds and stops with no loss of balance.
(1) Moderate impairment: Turns slowly, requires verbal cueing, requires several small steps to catch balance following turn and stop.
(0) Severe impairment: Cannot turn safely, requires assistance to turn and stop.

**6. Step over obstacle.** *<u>Instructions:</u> Begin walking at your normal speed. When you come to the shoebox, step over it, not around it, and keep walking.*
(3) Normal: Is able to step over box without changing gait speed; no evidence for imbalance.
(2) Mild impairment: Is able to step over shoe box, but must slow down and adjust steps to clear box safely.
(1) Moderate impairment: Is able to step over box but must stop, then step over. May require verbal cueing.
(0) Severe impairment: Cannot perform without assistance.

**7. Step around obstacles.** *<u>Instructions:</u> Begin walking at normal speed. When you come to the first cone (about 6' away), walk around the right side of it. When you some to the second cone (6' past first cone), walk around it to the left.*
(3) Normal: Is able to walk safely around cones safely without changing gait speed; no evidence of imbalance.
(2) Mild impairment: Is able to step around both cones, but must slow down and adjust steps to clear cones.
(1) Moderate impairment: Is able to clear cones but must significantly slow speed to accomplish task, or requires verbal cueing.
(0) Severe impairment: Unable to clear cones, walks into one or both cones, or requires physical assistance.

**8. Steps.** *<u>Instructions:</u> Walk up these stairs as you would at home.(i.e. using a rail if necessary. At the top, turn around and walk down.*
(3) Normal: Alternating feet, no rail.
(2) Mild impairment: Alternating feet, must use rail.
(1) Moderate impairment: Two feet to a stair, must use rail.
(0) Severe impairment: Cannot do safely.

**TOTAL SCORE**

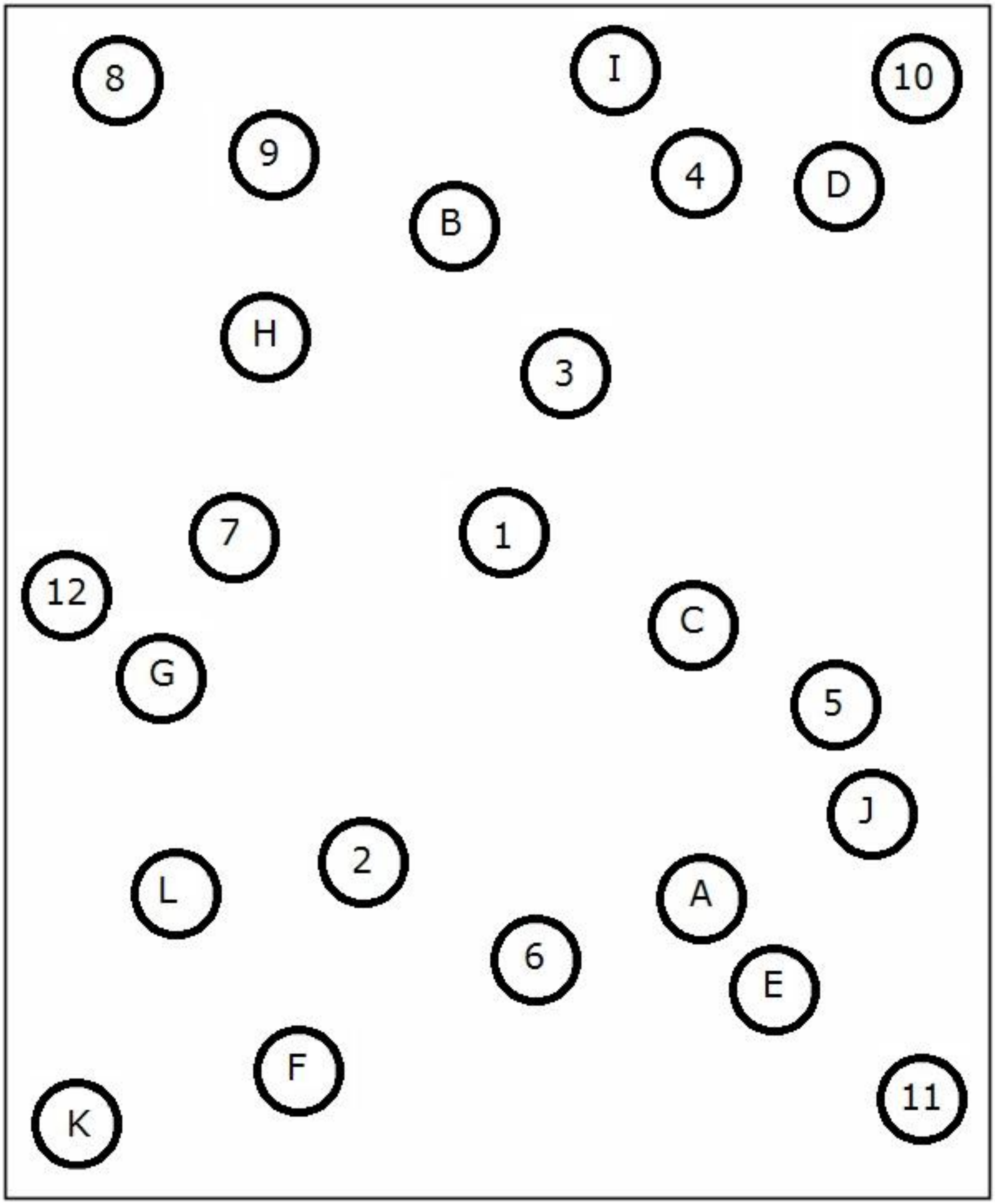
Admission:____________________ Date:______________________

Discharge:____________________ Date:______________________

Signature: _____________________ Designation: ___________________

# Trail Making Test Part B

Patient's Name: ______________________________ Date: ____________________



# Falls Efficacy Scale

Subject:____________________ Visit: _____________ Date:__________________

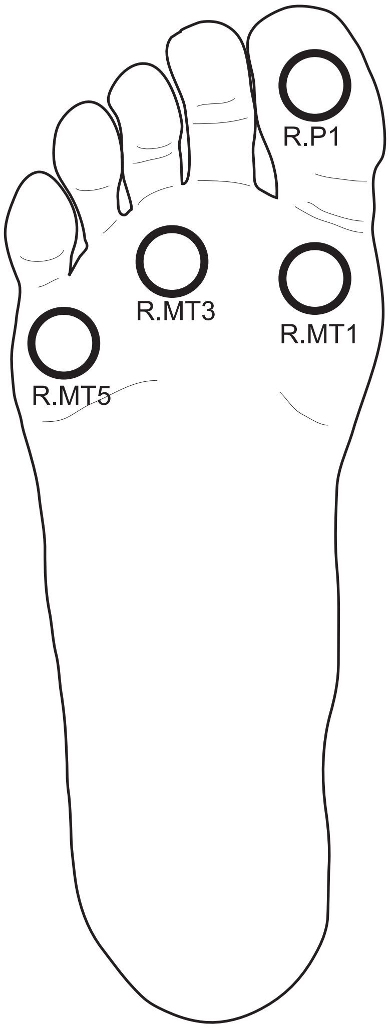
On a scale from 1 to 10, with 1 being very confident and 10 being not confident at all, how confident are you that you do the following activities without falling?

| **Activity:** | **Score:**<br>1 = very confident<br>10 = not confident at all |
|---|---|
| Take a bath or shower | |
| Reach into cabinets or closets | |
| Walk around the house | |
| Prepare meals not requiring carrying heavy or hot objects | |
| Get in and out of bed | |
| Answer the door or telephone | |
| Get in and out of a chair | |
| Getting dressed and undressed | |
| Personal grooming (i.e. washing your face) | |
| Getting on and off of the toilet | |
| **Total Score** | |

Adapted from Tinetti et al (1990)

Subject ID ____________________ Date ____________________ Pre / Post

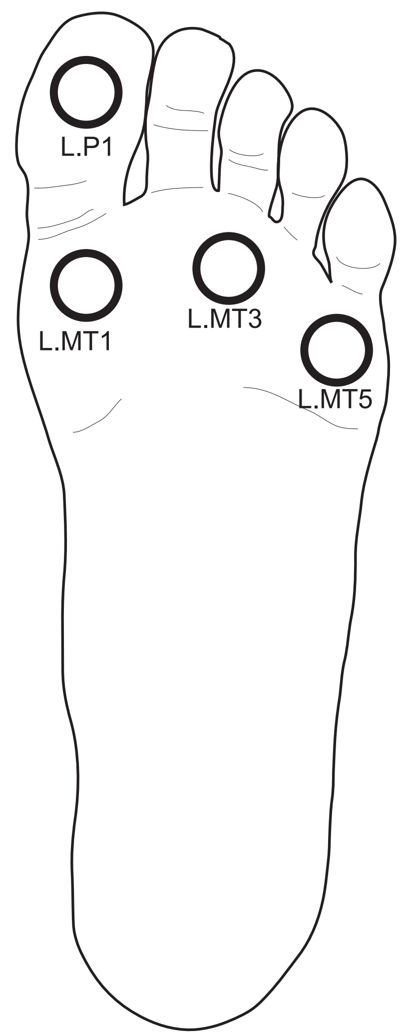
## Right Foot




Right Foot

| | R.P1 | R.MT1 | R.MT3 | R.MT5 |
|---|---|---|---|---|
| 0.07g | | | | |
| 0.40g | | | | |
| 2.0g | | | | |
| 4.0g | | | | |
| 10g | | | | |
| 300g | | | | |

## Left Foot




Left Foot

| | L.P1 | L.MT1 | L.MT3 | L.MT5 |
|---|---|---|---|---|
| 0.07g | | | | |
| 0.40g | | | | |
| 2.0g | | | | |
| 4.0g | | | | |
| 10g | | | | |
| 300g | | | | |

# Bibliography


[1] AM Tromp, SMF Pluijm, JH Smit, DJH Deeg, LM Bouter, and PTAM Lips. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *Journal of clinical epidemiology*, 54(8):837–844, 2001.

[2] Daniel A Sterling, Judith A O'Connor, and John Bonadies. Geriatric falls: injury severity is high and disproportionate to mechanism. *Journal of Trauma and Acute Care Surgery*, 50(1):116–119, 2001.

[3] Bruce H Alexander, Frederick P Rivara, and Marsha E Wolf. The cost and frequency of hospitalization for fall-related injuries in older adults. *American journal of public health*, 82(7):1020–1023, 1992.

[4] Centers for Disease Control et al. Injury prevention & control: data & statistics (wisqars). *Welcome to WISQARS (Web-based Injury Statistics Query and Reporting System. CDC Web site. http://www. cdc. gov/injury/wisqars/. Accessed May 15*, 2014.

[5] David M Buchner, M Elaine Cress, Edward H Wagner, Barbara J de Lateur, Robert Price, and Itamar B Abrass. The seattle ficsit/movelt study: the effect of exercise on gait and balance in older adults. *Journal of the American Geriatrics Society*, 41(3): 321–325, 1993.

[6] Michael A Province, Evan C Hadley, Mark C Hornbrook, Lewis A Lipsitz, J Philip Miller, Cynthia D Mulrow, Marcia G Ory, Richard W Sattin, Mary E Tinetti, Steven L Wolf, et al. The effects of exercise on falls in elderly patients: a preplanned meta-analysis of the ficsit trials. *Jama*, 273(17):1341–1347, 1995.

[7] Mary E Tinetti, Dorothy I Baker, Gail McAvay, Elizabeth B Claus, Patricia Garrett, Margaret Gottschalk, Marie L Koch, Kathryn Trainor, and Ralph I Horwitz. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *New England Journal of Medicine*, 331(13):821–827, 1994.

[8] David M Buchner, M Elaine Cress, Barbara J de Lateur, Peter C Esselman, Anthony J Margherita, Robert Price, and Edward H Wagner. The effect of strength and endurance training on gait, balance, fall risk, and health services use in community-living older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 52(4):M218–M224, 1997.

[9] Melinda M Gardner, M Clare Robertson, and A John Campbell. Exercise in preventing falls and fall related injuries in older people: a review of randomised controlled trials. *British journal of sports medicine*, 34(1):7–17, 2000.

[10] Laurence Z Rubenstein, Karen R Josephson, Peggy R Trueblood, Steven Loy, Judith O Harker, Fern M Pietruszka, and Alan S Robbins. Effects of a group exercise program on strength, mobility, and falls among fall-prone elderly men. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 55(6):M317–M321, 2000.

[11] Harry B Skinner, Robert L Barrack, and STEPHEN D COOK. Age-related decline in proprioception. *Clinical orthopaedics and related research*, 184:208–211, 1984.

[12] Philip D Sloane, Robert W Baloh, and Vicente Honrubia. The vestibular system in the elderly: clinical implications. *American journal of otolaryngology*, 10(6):422–429, 1989.

[13] Lars Larsson, Gunnar Grimby, and Jan Karlsson. Muscle strength and speed of movement in relation to age and muscle morphology. *Journal of Applied Physiology*, 46(3): 451–456, 1979.

[14] Bret H Goodpaster, Seok Won Park, Tamara B Harris, Steven B Kritchevsky, Michael Nevitt, Ann V Schwartz, Eleanor M Simonsick, Frances A Tylavsky, Marjolein Visser,

and Anne B Newman. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 61(10):1059–1064, 2006.

[15] Shu-Chen Li, Ulman Lindenberger, and Sverker Sikström. Aging cognition: from neuromodulation to representation. *Trends in cognitive sciences*, 5(11):479–486, 2001.

[16] Shmuel Springer, Nir Giladi, Chava Peretz, Galit Yogev, Ely S Simon, and Jeffrey M Hausdorff. Dual-tasking effects on gait variability: The role of aging, falls, and executive function. *Movement Disorders*, 21(7):950–957, 2006.

[17] Anthony J Bell, Janet K Talbot-Stern, and Annemarie Hennessy. Characteristics and outcomes of older patients presenting to the emergency department after a fall: a retrospective analysis. *The Medical Journal of Australia*, 173(4):179–182, 2000.

[18] Fuzhong Li, K John Fisher, Peter Harmer, Edward McAuley, and Nicole L Wilson. Fear of falling in elderly persons: association with falls, functional ability, and quality of life. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, 58 (5):P283–P290, 2003.

[19] Brian E Maki. Gait changes in older adults: predictors of falls or indicators of fear? *Journal of the American geriatrics society*, 45(3):313–320, 1997.

[20] Bruno J Vellas, Sharon J Wayne, Linda J Romero, Richard N Baumgartner, and Philip J Garry. Fear of falling and restriction of mobility in elderly fallers. *Age and ageing*, 26 (3):189–193, 1997.

[21] George F Fuller. Falls in the elderly. *American family physician*, 61(7):2159–68, 2000.

[22] K Kraemer, J Dewane, S Bobula, T Nelson, and Bryan Heiderscheit. The effects of a modified otago exercise program on gait speed and strength in community dwelling older adults. In *Wisconsin Physical Therapy Association Meeting*, 2009.

[23] Erwin B Montgomery and John T Gale. Mechanisms of action of deep brain stimulation (dbs). *Neuroscience & Biobehavioral Reviews*, 32(3):388–407, 2008.

[24] David H Benninger, Kazumi Iseki, Sarah Kranick, David A Luckenbaugh, Elise Houdayer, and Mark Hallett. Controlled study of 50-hz repetitive transcranial magnetic stimulation for the treatment of parkinson disease. *Neurorehabilitation and neural repair*, 26(9):1096–1105, 2012.

[25] Pablo Arias, Jamile Vivas, Kenneth L Grieve, and Javier Cudeiro. Controlled trial on the effect of 10 days low-frequency repetitive transcranial magnetic stimulation (rtms) on motor signs in parkinson's disease. *Movement Disorders*, 25(12):1830–1838, 2010.

[26] Y Danilov, M Tyler, and K Kaczmarek. A new approach to chronic tbi rehabilitation: Cranial nerve non-invasive neuromodulation (cn-ninm technology). In *Neurotrauma*, Phoenix, AZ, 2012.

[27] Yuri Danilov, Mitch Tyler, Kurt Kaczmarek, K Rust, and A Stubbotin. Neurorehabilitation of multiple sclerosis symproms using cranial nerve noninvasive neuromodulation (cn-ninm): controlled study. In *Society for Neuroscience Annual Meeting*, Washington, D.C., 2011.

[28] Mitchell E Tyler, Kurt A Kaczmarek, Kathy L Rust, Alla M Subbotin, Kimberly L Skinner, and Yuri P Danilov. Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: a randomized double blind controlled pilot trial. *Journal of neuroengineering and rehabilitation*, 11(1):1, 2014.

[29] Yuri P. Danilov, Mitchell E. Tyler, Kimberly Skinner, and Paul Bach-y Rita. Efficacy of electrotactile vestibular substitution in patients with bilateral and central balance loss. In *Conference Proceedings IEEE Engineering in Medicine and Biology Society*, pages S6605–S6609, 2006.

[30] Joseph C Wildenberg, Mitchell E Tyler, Yuri P Danilov, Kurt A Kaczmarek, and Mary E Meyerand. High-resolution fmri detects neuromodulation of individual brainstem nuclei by electrical tongue stimulation in balance-impaired individuals. *Neuroimage*, 56(4): 2129–2137, 2011.

[31] VK Beresovskii and KV Bayev. New locomotor regions of the brainstem revealed by means of electrical stimulation. *Neuroscience*, 26(3):863–869, 1988.

[32] KV Bayev, VK Beresovskii, TG Kebkalo, and LA Savoskina. Afferent and efferent connections of brainstem locomotor regions: study by means of horseradish peroxidase transport technique. *Neuroscience*, 26(3):871–891, 1988.

[33] Anne Shumway-Cook and Marjorie H Woollacott. *Motor control: theory and practical applications*. Lippincott Williams & Wilkins, 1995.

[34] Sergio Romero, Mark D Bishop, Craig A Velozo, and Kathye Light. Minimum detectable change of the berg balance scale and dynamic gait index in older persons at risk for falling. *Journal of geriatric physical therapy*, 34(3):131–137, 2011.

[35] Jeffrey M Hausdorff, Dean A Rios, and Helen K Edelberg. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Archives of physical medicine and rehabilitation*, 82(8):1050–1056, 2001.

[36] Jeffrey M Hausdorff, Helen K Edelberg, Susan L Mitchell, Ary L Goldberger, and Jeanne Y Wei. Increased gait unsteadiness in community-dwelling elderly fallers. *Archives of physical medicine and rehabilitation*, 78(3):278–283, 1997.

[37] Jennifer S Brach, Jaime E Berlin, Jessie M VanSwearingen, Anne B Newman, and Stephanie A Studenski. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. *Journal of neuroengineering and rehabilitation*, 2(1):1, 2005.

[38] Jennifer S Brach, Stephanie Studenski, Subashan Perera, Jessie M VanSwearingen, and Anne B Newman. Stance time and step width variability have unique contributing impairments in older persons. *Gait & posture*, 27(3):431–439, 2008.

[39] Catherine E Bauby and Arthur D Kuo. Active control of lateral balance in human walking. *Journal of biomechanics*, 33(11):1433–1440, 2000.

[40] Jesse C Dean, Neil B Alexander, and Arthur D Kuo. The effect of lateral stabilization on walking in young and old adults. *Biomedical Engineering, IEEE Transactions on*, 54(11):1919–1926, 2007.

[41] Shawn M O'Connor and Arthur D Kuo. Direction-dependent control of balance during walking and standing. *Journal of neurophysiology*, 102(3):1411–1419, 2009.

[42] Wilson C Hayes, ER Myers, SN Robinovitch, A Van Den Kroonenberg, AC Courtney, and TA McMahon. Etiology and prevention of age-related hip fractures. *Bone*, 18(1): S77–S86, 1996.

[43] John H Hollman, Francine M Kovash, Jared J Kubik, and Rachel A Linbo. Age-related differences in spatiotemporal markers of gait stability during dual task walking. *Gait & posture*, 26(1):113–119, 2007.

[44] Véronique Dubost, Reto W Kressig, Régis Gonthier, François R Herrmann, Kamiar Aminian, Bijan Najafi, and Olivier Beauchet. Relationships between dual-task related changes in stride velocity and stride time variability in healthy older adults. *Human movement science*, 25(3):372–382, 2006.

[45] Andrew W Priest, Kathleen B Salamon, and John H Hollman. Age-related differences in dual task walking: a cross sectional study. *Journal of neuroengineering and rehabilitation*, 5(1):1, 2008.

[46] Sibylle B Thies, James K Richardson, and James A Ashton-Miller. Effects of surface irregularity and lighting on step variability during gait:: A study in healthy young and older women. *Gait & posture*, 22(1):26–31, 2005.

[47] Matthew A Schrager, Valerie E Kelly, Robert Price, Luigi Ferrucci, and Anne Shumway-Cook. The effects of age on medio-lateral stability during normal and narrow base walking. *Gait & posture*, 28(3):466–471, 2008.

[48] Diane Manchester, Marjorie Woollacott, Niki Zederbauer-Hylton, and Oscar Marin. Visual, vestibular and somatosensory contributions to balance control in the older adult. *Journal of Gerontology*, 44(4):M118–M127, 1989.

[49] Steven Robbins, Edward Waked, and Jacqueline McClaran. Proprioception and stability: foot position awareness as a function of age and footware. *Age and Ageing*, 24(1): 67–72, 1995.

[50] Shawn M. O'Connor, Henry Z. Xu, and Arthur D. Kuo. Energetic cost of walking with increased step variability. *Gait & posture*, 36(1):102–107, 2012.

[51] Anne Schmitz, Amy Silder, Bryan Heiderscheit, Jane Mahoney, and Darryl G Thelen. Differences in lower-extremity muscular activation during walking between healthy older and young adults. *Journal of Electromyography and Kinesiology*, 19(6):1085–1091, 2009.

[52] Tibor Hortobágyi and Paul DeVita. Mechanisms responsible for the age-associated increase in coactivation of antagonist muscles. *Exercise and sport sciences reviews*, 34 (1):29–35, 2006.

[53] YP Danilov, ME Tyler, KL Skinner, RA Hogle, and P Bach-y Rita. Efficacy of electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *Journal of Vestibular Research*, 17(2, 3):119–130, 2007.

[54] Jerome S Tobis, Sibylle Reinsch, James M Swanson, Mark Byrd, and Ted Scharf. Visual perception dominance of fallers among community-dwelling older adults. *Journal of the American Geriatrics Society*, 33(5):330–333, 1985.

[55] Antonia K Coppin, Anne Shumway-Cook, Jane S Saczynski, Kushang V Patel, Alessandro Ble, Luigi Ferrucci, and Jack M Guralnik. Association of executive function and performance of dual-task physical tests among older adults: analyses from the inchianti study. *Age and ageing*, 35(6):619–624, 2006.

[56] P Forizetti, V Panzer, and M Reding. Use of computerized dynamic posturography in the assessment of elderly fallers. *Neurorehabilitation and Neural Repair*, 14:83, 2000.

[57] Mary Jo Gibson, Robert O Andres, B Isaacs, T Radebaugh, and J Wormpetersen. The prevention of falls in later life-a report of the kellogg-international-work-group on the prevention of falls by the elderly. *Danish Medical Bulletin*, 34:1–24, 1987.

[58] Anne Shumway-Cook, Margaret Baldwin, Nayak L Polissar, and William Gruber. Predicting the probability for falls in community-dwelling older adults. *Physical therapy*, 77(8):812–819, 1997.

[59] JA Zeni, JG Richards, and JS Higginson. Two simple methods for determining gait events during treadmill and overground walking using kinematic data. *Gait & posture*, 27(4):710–714, 2008.

[60] J Perry and J Burnfield. *Gait analysis: Normal and Pathological Function.* Slack Incorporated, 2nd edition, 2010.

[61] Fay B Horak, Charlotte L Shupert, and Alar Mirka. Components of postural dyscontrol in the elderly: a review. *Neurobiology of aging*, 10(6):727–738, 1989.

[62] John J Jeka, Leslie K Allison, and Tim Kiemel. The dynamics of visual reweighting in healthy and fall-prone older adults. *Journal of motor behavior*, 42(4):197–208, 2010.

[63] Yang Wang and Manoj Srinivasan. Stepping in the direction of the fall: the next foot placement can be predicted from current upper body state in steady-state walking. *Biology Letters*, 10(9):20140405, 2014.

[64] Jason R Franz, Carrie A Francis, Matthew S Allen, Shawn M O'Connor, and Darryl G Thelen. Advanced age brings a greater reliance on visual feedback to maintain balance during walking. *Human movement science*, 40:381–392, 2015.

[65] Hal H Atkinson, Caterina Rosano, Eleanor M Simonsick, Jeff D Williamson, Cralen Davis, Walter T Ambrosius, Stephen R Rapp, Matteo Cesari, Anne B Newman, Tamara B Harris, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 62(8):844–850, 2007.

[66] Gabor Abellan Van Kan, Y Rolland, S Andrieu, J Bauer, O Beauchet, M Bonnefoy, M Cesari, LM Donini, S Gillette-Guyonnet, M Inzitari, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an international academy on nutrition and aging (iana) task force. *The journal of nutrition, health & aging*, 13(10):881–889, 2009.

[67] Sue Lord, Tracey Howe, Julia Greenland, Linda Simpson, and Lynn Rochester. Gait variability in older adults: a structured review of testing protocol and clinimetric properties. *Gait & posture*, 34(4):443–450, 2011.

[68] John H Hollman, Katherine B Childs, Megan L McNeil, Amy C Mueller, Christopher M Quilter, and James W Youdas. Number of strides required for reliable measurements of pace, rhythm and variability parameters of gait during normal and dual task walking in older individuals. *Gait & posture*, 32(1):23–28, 2010.

[69] Tammy M Owings and Mark D Grabiner. Variability of step kinematics in young and older adults. *Gait & posture*, 20(1):26–29, 2004.

[70] Brook Galna, Sue Lord, and Lynn Rochester. Is gait variability reliable in older adults and parkinson's disease? towards an optimal testing protocol. *Gait & posture*, 37(4): 580–585, 2013.

[71] JB Dingwell, JP Cusumano, PR Cavanagh, and D Sternad. Local dynamic stability versus kinematic variability of continuous overground and treadmill walking. *Journal of biomechanical engineering*, 123(1):27–32, 2001.

[72] S Okada, Kazufumi Hirakawa, Yoshihiro Takada, and Hiroshi Kinoshita. Relationship between fear of falling and balancing ability during abrupt deceleration in aged women having similar habitual physical activities. *European journal of applied physiology*, 85 (6):501–506, 2001.

[73] Koutatsu Nagai, Minoru Yamada, Kazuki Uemura, Buichi Tanaka, Shuhei Mori, Yosuke Yamada, Tomoki Aoyama, Noriaki Ichihashi, and Tadao Tsuboyama. Effects of fear of falling on muscular coactivation during walking. *Aging clinical and experimental research*, 24(2):157–161, 2012.

[74] Carrie A Francis, Jason R Franz, Shawn M O'Connor, and Darryl G Thelen. Gait variability in healthy old adults is more affected by a visual perturbation than by a cognitive or narrow step placement demand. *Gait & posture*, 42(3):380–385, 2015.

[75] K Falconer and DA Winter. Quantitative assessment of co-contraction at the ankle joint in walking. *Electromyography and clinical neurophysiology*, 25(2-3):135, 1985.

[76] Katherine S Rudolph, Michael J Axe, Thomas S Buchanan, John P Scholz, and Lynn Snyder-Mackler. Dynamic stability in the anterior cruciate ligament deficient knee. *Knee Surgery, Sports Traumatology, Arthroscopy*, 9(2):62–71, 2001.

[77] Mary E Tinetti, Donna Richman, and Lynda Powell. Falls efficacy as a measure of fear of falling. *Journal of gerontology*, 45(6):P239–P243, 1990.

[78] Katherine Berg, Sharon Wood-Dauphinee, and JI Williams. The balance scale: reliability assessment with elderly residents and patients with an acute stroke. *Scandinavian journal of rehabilitation medicine*, 27(1):27–36, 1995.

[79] Cheryl D Ford-Smith, Jean F Wyman, RK Elswick, Theresa Fernandez, and Roberta A Newton. Test-retest reliability of the sensory organization test in noninstitutionalized older adults. *Archives of physical medicine and rehabilitation*, 76(1):77–81, 1995.

[80] RJ St George, JG Nutt, KJ Burchiel, and FB Horak. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in pd. *Neurology*, 75(14): 1292–1299, 2010.

[81] Mitchell E Tyler, Yuri P Danilov, JC Wildenberg, and M. Elizabeth Meyerand. Neural pathways in non-invasive neuromodulation. In *Proceedings of the Society for Neuroscience Annual Meeting*, November 2008.

[82] Diane M Wrisley, Marilee J Stephens, Shaun Mosley, Adam Wojnowski, Jordan Duffy, and Robert Burkard. Learning effects of repetitive administrations of the sensory organization test in healthy young adults. *Archives of physical medicine and rehabilitation*, 88(8):1049–1054, 2007.

[83] Judith A. Dewane. *The relationship between postural control, gait variability and cognition, and their association to falls risk*. PhD thesis, University of Wisconsin-Madison, 2009.

[84] DM Connelly, BK Thomas, SJ Cliffe, WM Perry, and RE Smith. Clinical utility of the 2-minute walk test for older adults living in long-term care. *Physiotherapy Canada*, 61 (2):78–87, 2009.

[85] Subashan Perera, Samir H Mody, Richard C Woodman, and Stephanie A Studenski. Meaningful change and responsiveness in common physical performance measures in older adults. *Journal of the American Geriatrics Society*, 54(5):743–749, 2006.

[86] Khalid A Alahmari, Gregory F Marchetti, Patrick J Sparto, Joseph M Furman, and Susan L Whitney. Estimating postural control with the balance rehabilitation unit: measurement consistency, accuracy, validity, and comparison with dynamic posturography. *Archives of physical medicine and rehabilitation*, 95(1):65–73, 2014.

[87] Federica Tamburella, Giorgio Scivoletto, Marco Iosa, and Marco Molinari. Reliability, validity, and effectiveness of center of pressure parameters in assessing stabilometric platform in subjects with incomplete spinal cord injury: a serial cross-sectional study. *Journal of neuroengineering and rehabilitation*, 11(1):1, 2014.

[88] Vimonwan Hiengkaew, Khanitha Jitaree, and Pakaratee Chaiyawat. Minimal detectable changes of the berg balance scale, fugl-meyer assessment scale, timed "up & go" test, gait speeds, and 2-minute walk test in individuals with chronic stroke with different degrees of ankle plantarflexor tone. *Archives of physical medicine and rehabilitation*, 93 (7):1201–1208, 2012.

[89] Claudia Bartels, Martin Wegrzyn, Anne Wiedl, Verena Ackermann, and Hannelore Ehrenreich. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. *BMC neuroscience*, 11(1):1, 2010.

[90] Penny C Grabiner, S Tina Biswas, and Mark D Grabiner. Age-related changes in spatial and temporal gait variables. *Archives of physical medicine and rehabilitation*, 82 (1):31–35, 2001.

[91] Jeffrey M Hausdorff. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. *Human movement science*, 26(4):555–589, 2007.

[92] Jorunn L Helbostad and Rolf Moe-Nilssen. The effect of gait speed on lateral balance control during walking in healthy elderly. *Gait & posture*, 18(2):27–36, 2003.

[93] Nobuou Matsusaka. Control of the medial-lateral balance in walking. *Acta Orthopaedica Scandinavica*, 57(6):555–559, 1986.