ANTICHOLINERGIC DRUG AND WHITE MATTER HYPERINTENSITY EFFECTS ON BALANCE AND GAIT IN OLDER ADULTS

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Alison Lyn Sukits

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This thesis was presented

by

Alison Lyn Sukits

It was defended on

September 2, 2011

and approved by

Howard Aizenstein, M.D., Ph.D., Associate Professor, Department of Psychiatry

Robert Nebes, Ph.D., Professor, Department of Psychiatry

Subashan Perera, Ph.D., Associate Professor, Department of Medicine

Mark S. Redfern, Ph.D., Professor, Department of Bioengineering

Thesis Advisor: Rakié Cham, Ph.D., Associate Professor, Department of Bioengineering

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Alison Lyn Sukits, MS

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Falls are a major cause of injury in older adults, leading to decreased quality of life and high economic cost. While the cause of falls is multi-dimensional, they have been linked to several characteristics seen in older adults. Specifically, this research focused on relating the use of medications and cerebrovascular changes with normal aging to changes in balance and gait, thus possibly increasing fall risk. The medications of interest were those with anticholinergic properties whose drug mechanism was to block the neurotransmitter acetylcholine. Medication use was measured using blood serum anticholinergic activity levels (SAA) of active receptor inhibitors. The cerebrovascular changes included those associated with white matter hyperintensities (WMH) in five regions of interest in the deep cerebral white matter detected by magnetic resonance imaging. The exact mechanism of action to negatively impact balance and gait is not well-known.

Balance was assessed using measures of sway or center of pressure (COP) while gait was assessed using spatiotemporal variability parameters. Forty-eight participants, aged 65 to 80, were recruited. Balance and gait protocols were performed under single and dual-task digit recall conditions. Overall, performing tasks while standing or walking caused increased sway and temporal variability, respectively. When standing with eyes closed and not performing a task, participants' sway increased with increasing WMH. However, no relationship was found with SAA. During gait, a positive relationship was found between WMH and cadence, stance time,

and step time variability, but only within two WMH regions. No relationships with SAA were identified. The lack of more correlations between the variables of interest could be attributed to the lack of variability in WMH and SAA along with the overall excellent health of the participants. These results indicate the potential for negative effects on balance and gait with healthy neural aging and anticholinergic drug use. Further investigations must be conducted to better understand the mechanism of action causing the negative impact on balance and gait. Once understood, better care can be taken to monitor medication use and provide therapeutic training to people at a higher risk for falls as related to medication burden and increased WMH with age.

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NOMENCLATURE

NT	No dual-task condition
F	Forward dual-task condition
B	Backward dual-task condition
SAA	Serum anticholinergic activity
WMH	White matter hyperintensity
FLAIR	Fast fluid-attenuated inversion recovery
MPRAGE	Magnetization-prepared rapid acquisition gradient-echo
WMH ALL	White matter hyperintensities in all tracts
CHOL	White matter hyperintensities in tracts containing cholinergic fibers
NON-CHOL	White matter hyperintensities in tracts containing non-cholinergic fibers
AACC	White matter hyperintensities in the left and right anterior thalamic radiations and the left and right corticospinal tracts
SS	White matter hyperintensities in the left and right superior longitudinal fasciculus
CC	White matter hyperintensities in the frontal and occipital regions of the corpus callosum
DTI	Diffusion tensor imaging
FA	Fractional anisotropy

EO	Eyes open
EC	Eyes closed
ML	Medial-lateral direction
AP	Anterior-posterior direction
COP_{ML}	Center of pressure in the medial-lateral direction
COP_{AP}	Center of pressure in the anterior-posterior direction
AP RMS	Center of pressure root mean squared in the anterior-posterior direction
ML RMS	Center of pressure root mean squared in the medial-lateral direction
AP VEL	Mean sway velocity in the anterior-posterior direction
ML VEL	Mean sway velocity in the medial-lateral direction
PL	Path length
ρ	Spearman rank correlation coefficient
r	Pearson correlation coefficient
Average GS	Average gait speed
STV	Stance time variability
DSV	Double support time variability
SEV	Step time variability
CV	Cadence variability

PREFACE

This work would not have been possible without the help and support of my committee members, Dr. Rakié Cham, Dr. Howard Aizenstein, Dr. Robert Nebes, Dr. Subashan Perera, and Dr. Mark Redfern. I am especially thankful for my advisor Dr. Rakié Cham and the principal investigator of this study, Dr. Robert Nebes, for giving me the opportunity to work on this project and for providing me with so much support throughout my graduate career. This work was supported by research grants from the National Institutes of Health and National Institutes of Aging (R01 AG030452).

1.0 INTRODUCTION

With a steadily increasing population of older adults in the United States, falls in the elderly have become a well-known health problem. It has been estimated that one in three community-dwelling adults over the age of 65 experiences a fall at least once a year (Hausdorff et al., 2001). This risk increases to one in two adults when looking at those over the age of 80 (Inouye et al., 2009). Falls are associated with several adverse conditions and are often serious. In community-dwelling fallers over the age of 65, decreased mobility and loss of independence are associated with approximately 20-30% of these falls (Sterling et al., 2001), leading to decreased quality of life. In 2007, falls were the leading cause of death from unintentional injuries in adults over the age of 65 (NCIPC, 2007). With such a high incidence of falls, the economic burden is also significant. In 2000, the direct medical cost estimate in the United States for all falls in those over 65 years was $19.2 billion (American Geriatrics Society, British Geriatrics Society, American Academy of Orthopaedic Surgeons Panel on Falls Prevention, 2001), and this estimate is expected to rise to $54.9 billion by 2020 (Englander et al., 1996). The United States Census Bureau has predicted that the population of people aged 65 and over will double by 2030 and those aged 80 and older will increase five times by 2050 (USCB, 2004). These statistics demonstrate that the issues associated with such a high fall incidence in this growing population will continue to be a major health, social, and economic problem in the United States without intervention or prevention.

The cause of falls in the aging population is multi-dimensional and can be attributed to many different factors. Factors shown to increase fall risk have been classified as *intrinsic* or *extrinsic* (Naqvi et al., 2009). *Extrinsic* factors are typically modifiable environmental factors such as poor lighting, lack of safety equipment, and loose carpeting. *Intrinsic* factors include but are not limited to age, muscle weakness, balance or gait deficiency, fear of falling, cognitive impairment and brain dysfunction, and the use of high-risk medications (Clyburn and Heydemann, 2011). Older adults will typically experience one or more of these risk factors, and previous work has demonstrated a cumulative effect when the number of risk factors increases. Community-dwelling adults over the age of 65 increase their fall risk from 27% to 78% when the number of applicable risk factors increases to four or more (Tinetti et al., 1988). While some intrinsic factors such as age or gender cannot be modified, interventions specific to other intrinsic factors, such as modifying medication use and strength training may be of importance for minimizing fall risk in the aging population. By understanding the mechanisms and consequences of factors such as medication burden, muscle weakness, and cognitive decline on performance and fall risk, training programs and more effective patient management may be developed to help minimize and prevent falls in older adults.

1.1 BALANCE, GAIT AND THEIR RELATIONSHIP TO FALLS

Risk factors for falls in older adults investigated in the present work include those related to postural stability during standing balance and gait characteristics during over ground walking.

1.1.1 Postural Control and Balance

Maintaining balance requires integration by the central nervous system (CNS) of three different systems: visual, proprioceptive, and vestibular. It has been shown that together, these systems work in a feedback loop to maintain balance and produce counteractive motions to the constant displacement of gravity acting on a person during upright stance (Johannson, 1991; Horak & Macpherson, 1996; Peterka, 2002). Vision detects head orientation with respect to the surrounding environment, proprioception detects lower limb orientation with respect to the ground or support surface, and the vestibular system detects orientation changes of the head due to the force of gravity (Peterka, 2002). While there is a certain level of redundancy across the systems, perturbing one or two of the systems requires combined efforts and adaptation of the remaining systems so that a person will remain upright. This method, better known as sensory re-weighting, allows the body to dynamically react to the ever-changing demands of the environment (Peterka, 2002; Mahboobin et al., 2005; Maurer et al., 2006). An example of the loss of one system would be asking someone to stand with his or her eyes closed. By removing the visual input to the CNS, the vestibular system and proprioception must re-weight their responsibilities and take over the loss of visual input while still keeping the body upright (Peterka, 2002). The interactions of these three systems then, are ultimately determined by their health and integration, the information available to them, and the environmental cues from the surroundings (Redfern et al., 2001).

Decrements in balance in older adults have been classified as an intrinsic risk for falls. Previous research has demonstrated a significant difference between older adults classified as fallers and non-fallers in clinical assessments such as an increased score on the Timed Up and Go Test (Podsiadlo et al., 1991; Gunter et al., 2000) and a decreased score on the Berg Balance

Scale (Berg et al., 1992; Shumway-Cook, 1997) in fallers compared to non-fallers. These clinical assessments are widely utilized, easily administered, and often used as a guideline for intervention and assessing intervention effectiveness. While it is beneficial to understand the differences between these groups and identify those at a higher risk for a first or recurrent fall, these assessments are subjective, self-paced and controlled in a predictable environment (Desai et al., 2010). Quantitative analyses of postural control using validated laboratory protocols such as dynamic posturography have also shown a decline in balance performance with age (Peterka & Black, 1990; Ledin et al., 1990; Wolfson et al., 1992). The increased instability in older adults with the changes observed in these analyses can be linked back to an increased fall risk in this population.

As mentioned previously, the three systems must be working properly to maintain an upright posture and avoid losing balance. It is the malfunction of one of these systems that would lead to the decline in performance during a balance task (Speers et al., 2002). While the exact mechanism of decline is not particularly known, each system can be analyzed independently for change. Changes with age to the vestibular system can include a decrease in the number of hair cells in the individual organs within the system or a decrease in conducting fibers located in the vestibular nerve (Rosenhall, 1973; Bergstrom, 1973). With regards to vision, it has been shown that older adults experience a decrease in visual acuity and sensitivity during low frequency motion (Sekuler & Hutman, 1980). Studies have even shown that older adults rely more on visual information to maintain balance during quiet stance (Sheldon, 1963; Alexander, 1994). Finally, peripheral neuropathy, leading to decreased proprioception, is also common in older adults. One in five older adults suffers from peripheral neuropathy, thus decreasing the sensory feedback from proprioception, increasing the risk of poor balance performance and increasing

the risk of falls (Richardson, 1996). Degradation in one or more of these systems in addition to decreased neural processing and increased muscle weakness with age will all have a negative impact on postural control and standing balance in older adults, increasing the likelihood of falls.

1.1.2 Spatiotemporal Gait Characteristics during Normal Walking

In addition to postural control during stance, spatiotemporal gait characteristics are also important in understanding fall risk in older adults. Previous research has shown several links between falls and these variables of interest (Beauchet et al., 2005; Dubost, et al. 2006). Gait speed has been shown to contribute to falls in older adults when decreased during normal walking (Luukinen et al., 1995; Cesari et al., 2005; Montero-Odasso et al., 2005). This decrease in speed, however, may actually be an indicator for other functionally limiting co-morbidities (Studenski, 2009). Gait variability has also been shown to predict falls and decreased physical function in older adults (Hausdorff, 2007; Brach et al., 2008). Gait variability is a measure of intra-individual fluctuation in a particular variable of gait from one step to the next. It is said to represent alterations to the intrinsic control mechanisms of gait from a decline in several factors including changes in the CNS (Maki, 1997; Brach et al., 2005). Gait variability has been shown to increase with age. Increased variability, such as in double support or stance time, has been directly associated with mobility disability and fall risk in older adults (Hausdorff et al., 1997; Maki, 1997; Hausdorff et al., 2001; Brach et al., 2007). Increased gait variability is a direct reflection of an inconsistent pattern of walking due to a reduction in postural control (Hollman et al., 2007).

1.2 RELATIONSHIP BETWEEN ANTICHOLINERGIC BURDEN AND FALL RISK

One intrinsic factors shown to impact the risk of falls in adults over the age of 65 is medication use (Naqvi et al., 2009). Specific classes of medications commonly prescribed to the aging population have been previously demonstrated as an increased risk for falls including psychotropics such as benzodiazepines and antidepressants (Monane & Avorn, 1996; Cumming, 1998; Landi et al., 2005; Howland, 2009), cardiovascular drugs such as nitrates (Cumming, 1998), and non-steroidal anti-inflammatory drugs (Cumming, 1998). Another key drug group that is commonly prescribed to older adults and available over-the-counter is a class of drugs known as anticholinergics or antimuscarinics. Drugs exhibiting anticholinergic properties act by inhibiting the neurotransmitter acetylcholine from binding to the muscarinic receptors in the brain. The target receptors are primarily located on motor end plates of skeletal muscle and autonomic effector cells innervated by the parasympathetic nerves. The targets' cell bodies are at their highest densities within the CNS, hippocampus, cortex, and thalamus (Brunton et al., 2011). Research has shown that there are more than 600 anticholinergic drugs available (Tune, 2001) with 11% of these drugs commonly prescribed to the older adult population (Tollefson et al., 1991). Examples of these commonly prescribed drugs include diphenhydramine, codeine, diazepam, prednisolone, and clindamycin (Tune et al., 1992).

Anticholinergics target several different organ systems including the CNS, eyes, cardiovascular and respiratory systems, and gastrointestinal and genitourinary tracts. There are many beneficial clinical applications of these drugs including motion sickness control, tremor reduction in Parkinson's patients, bronchodilation during allergic reaction and asthma attacks, cardiac rhythm regulation, and treatment of urinary incontinence. However, successful treatment of these systems is typically accompanied by adverse drug reactions (ADRs) including lethargy,

hallucinations, amnesia, dry eyes, fibrillation, and significant urine retention (Katzung et al., 2009). In addition to the ADRs mentioned, research has also demonstrated that the use of muscarinic blocking drugs has been associated with a decline in cognitive function including working memory, episodic memory, attention, and processing speed (Sunderland et al., 1988; Flicker et al., 1992; Molchan et al., 1992; Mulsant et al., 2003; Landi, 2007). ADRs related to anticholinergic drug use are often enhanced in older adults as they are typically taking multiple medications at once. In a study on nursing home patients, 21-32% of residents were taking two or more drugs with anticholinergic properties (Blazer et al., 1983), putting them at an increased risk for multiple ADRs and decreased quality of life.

With an increase in the number of medications taken by older adults and the high number of drugs exhibiting anticholinergic properties available by prescription and over-the-counter, it should be of concern that community-dwelling older adults are exposed to anticholinergic ADRs that may impact daily living and potentially place them in a life-threatening situation. In fact, anticholinergic medications have been linked to falls in older adults (Landi et al., 2005; Aizenberg et al., 2002; Wilson, 2011). However, these studies were derived from hospital or residential care facility inpatient fall histories, not from community-dwelling older adults whose medication burden may be just as significant if not worse because of access to medications. With regard to the population of interest, motor impairments while taking anticholinergics have been reported. Cao and colleagues (2008) found that in older women, anticholinergic burden was associated with decreased gait speed and decline in ability to balance in side-by-side, semi-tandem, and tandem stance for 10 seconds. Nebes and colleagues (2007) also found decreased gait speed with increased anticholinergic medication levels. Landi and others (2007) showed a significant decrease in average score on the Short Physical Performance Battery (SPPB) in

anticholinergic drug users over the age of 80. Finally, Hilmer (2007) demonstrated that increased anticholinergic drug burden in community-dwelling adults aged 70 to 79 is associated with decreased physical function as measured by the Health ABC performance score.

While insight into the relationship between anticholinergic medications and fall risk is important, previous research demonstrating this relationship is limited to qualitative and subjective measures of balance and gait. Additionally, the mechanism of action of anticholinergic medications to inflict decline in both balance and gait is unknown. To better understand the mechanism of action, more quantitative measures of balance and gait, outside of simple gait speed, are needed to identify the potential impact of anticholinergic medications on balance and gait. Dr. Robert Nebes, the primary investigator of this research project, has shown in completed pilot work that increased levels of anticholinergic medications were significantly associated with increased sway in the medial-lateral direction without a concurrent task and increased stride time variability in the presence of a concurrent task. This pilot work was completed with the use of only eight participants. The significance of these results in such a small sample size is direct motivation to pursue this research on a larger sample of participants to better understand the impact of anticholinergic medications on balance and gait.

1.3 RELATIONSHIP BETWEEN WHITE MATTER HYPERINTENSITIES AND FALL RISK

Other points of interest in the aging population and fall risk are age-related changes in the brain. Just as anticholinergic drugs act on the brain to produce decrements in motor control and physical performance, changes within the brain have also been linked to decreased motor

function in older adults. One group of changes that have been identified as markers of cerebrovascular disease are better known as white matter hyperintensities (WMH) which are found in the deep cerebral white matter. These areas are represented as high signal intensities on magnetic resonance imaging (MRI) and are common in both normal and cognitively impaired older adults (Appel et al., 2009; Ota et al., 2010). The deep vessels located in the white matter experience hyperprofusion and disruption of the blood-brain barrier, leading to chronic plasma leakage and lesion formation within these areas (Pantoni & Garcia, 1997; O'Sullivan, 2002; Topakian, 2010). The physiological consequences of developing WMH have been associated with demyelination, loss of axons, gliosis, and dilation of the periventricular space (Ota et al., 2010). Interestingly, 11-21% of healthy adults aged 64 have visible WMH on MRI, and 94% of healthy adults show similar results by the age of 82 (Debette & Marcus, 2010). In addition to age, several health conditions serve as risk factors for developing WMH including prior myocardial infarction or stroke, hypertension, elevated cholesterol, and heart disease (Bretler, 1994).

Since WMH are associated with neural changes in both healthy older adults and those with co-morbidities, it is of interest to understand how these changes may affect cognitive and physical function. As with anticholinergic drugs, WMH have been associated with declines in cognitive function (Bretler, 1994; Debette & Marcus, 2010). Of greater interest is their impact on balance and gait. Several studies have been conducted into understanding the changes in physical function in older adults with WMH, correlating this to fall risk. As with increased anticholinergic drug use, decreases in performance during the SPPB have been shown with increased WMH levels (Benson et al. 2002; Wolfson et al. 2005). Murray and colleagues (2010) found a decrease in visual gait performance and gait speed with an increased level of WMH, suggesting that

WMH result in overall motor slowing. Another study looking at auditory cued step-initiation and WMH found greater processing time to initiate a response with higher levels of WMH, indicating a risk for decreased mobility and increased fall potential (Sparto et al., 2008). Finally, Rosano and others (2006) showed decreased gait speed and increased stride and double support time to be associated with increased WMH, indicating deteriorations in gait with the presence of cerebrovascular changes and aging. Other than speculation as in with anticholinergic medications, the exact mechanism of WMH for eliciting an impact on balance and gait remains unknown. Additionally, other than the work of Sparto and colleagues (2008), and Novak and colleagues (2009), current research has looked only into overall brain WMH. It is of interest to identify if specific regions of the brain associated with motor, executive, and cognitive function are more related to decrements in balance and gait than overall WMH.

1.4 INTERACTION EFFECTS OF ANTICHOLINERGIC DRUGS AND WHITE MATTER HYPERINTENSITIES

With evidence pointing to several detrimental effects when taking anticholinergic drugs or in the presence of WMH with age, it should also be of interest to investigate any potential relationship between the combination of these independent factors. Previous research has demonstrated a link between individuals taking anticholinergic drugs and the presence of WMH with a decline in cognition (Nebes et al., 2005). According to Bocti and colleagues (2005), one possible mechanism of cognitive decline is the interference of WMH with cholinergic pathways located in the white matter. The location of these pathways leaves them susceptible to vascular lesions associated with WMH (Seldon, 1998). Both animal and human models have shown an increased

sensitivity to anticholinergic drugs such as scopolamine when accompanied by the interference of cholinergic pathways in the aging brain (Flicker et al., 1992; Ray et al., 1992). Another mechanism of action when combining the effects of WMH with anticholinergic drugs could be the increased permeability of the blood-brain barrier. Starr and colleagues (2003) showed a positive relationship between permeability and WMH. An increase in WMH in healthy adults resulted in an increased permeability. As a result, anticholinergic medications may be able to better penetrate the neural tissue and cause greater effects when taken by older adults with high levels of WMH. With evidence in cognitive decline from combined effects, it may be suggested that the increased fall risk associated with WMH or anticholinergic drugs alone may actually be amplified when occurring simultaneously in otherwise healthy older adults.

1.5 DUAL-TASK EFFECTS ON BALANCE AND GAIT

Of added interest in the participant population recruited for this proposed work is the impact of altered attention on balance and gait. As stated previously, both anticholinergic drugs and WMH have been associated with cognitive decline including slowing of processing and changes in attention (Sunderland et al., 1988; Flicker et al., 1992; Molchan et al., 1992; Mulsant et al., 2003; Landi, 2007; Appel et al., 2009; Ota et al., 2010). While this may also be attributed to healthy aging where it is common to see a decrease in executive function (Herman et al., 2010), it is of interest to see if there is a correlation between high levels of anticholinergic drugs and WMH with attention and performance during a dual-task paradigm. A dual-task paradigm is used to investigate the cognitive demands of postural control while performing a separate nonpostural task such as repeating numbers or reading. The thought is that the control of posture and

maintaining upright stance must compete with the secondary exercise for the available central resources (Prado et al., 2007). Previous research has shown that with age, control of balance and gait becomes difficult as there is a decline in the sensorimotor information available. This then requires more attention to safely maintain an upright posture (Li et al., 2001; Bloem et al., 2003). Falls in older adults have been associated with activities requiring divided attention between two tasks such as walking while talking (The Prevention of Falls in Later Life, 1987; Bergland et al., 1998).

Several studies have revealed an increase in postural sway while performing a cognitive challenge task under quiet stance (Maylor & Wing, 1996; Shumway-Cook & Woollacott, 2000; Teasdale & Simoneau, 2001). Others have identified decreased gait speed and increased gait variability when walking while performing a cognitive task (Hausdorff et al., 2003; Sheridan et al., 2003; Beauchet et al., 2005). Interestingly, Bloem and colleagues (2001) found that older adults experiencing a cognitive task while asked to maintain balance use what they have called a 'posture first' strategy. With this, older adults prioritize maintaining balance over successful completion of the secondary task, potentially trying to avoid falling. With these results, it can be concluded that there must be some aspect of attention and cognition responsible for execution of both balance and gait.

1.6 SUMMARY

With previous work documenting declines in motor performance, physical function and increased fall risk with anticholinergic drug use and WMH, a thorough analysis must be conducted to better understand the impact of these drugs and neural changes on balance and gait

in community-dwelling older adults. Specifically, looking at postural sway and temporal gait characteristics, the effects of these intrinsic factors on balance and gait can be quantitatively obtained, revealing potential underlying mechanisms of how anticholinergic medications and WMH are related to fall risk in older adults. These assessments will be conducted under both control and cognitive tasks. By understanding the characteristics of each participant's balance and gait prior to and during a cognitive task, there may be a better understanding of functional performance under cognitive loads but also the correlation of this performance to anticholinergic drugs and WMH. Finally, since WMH have been shown with normal aging, it is also of interest to understand the relationship between older adults currently taking anticholinergic drugs and their levels of WMH as detected by MRI. Understanding these two risk factors for falls in the older population may allow clinicians to better medicate, educate, and intervene with their patient populations to reduce the risk and number of falls.

1.7 SPECIFIC AIMS

The long term goal of this project is to better understand the possible mechanisms by which decrements in balance and gait are associated with anticholinergic medications, white matter hyperintensities, and their combined effects. With knowledge of how change is inflicted, specific training protocols and medication monitoring can be better conducted to improve physical function and minimize the potential risk for falls in older adults. Understanding these factors and their relationships to balance and gait may provide additional insight into the mechanisms of action. Previous work is limited to qualitative analyses, simple measures, and the lack of combining these factors of interest. With this, the overall purpose of this research study was to

understand the relationships between anticholinergic burden, WMH, and their combined effects on balance outcome measures, gait speed, and temporal gait variability.

The first focus of this research project is to understand the impact of anticholinergic medications on balance and gait. Specifically, anticholinergic medications have been shown to impact cognitive function. Thus, it is likely that anticholinergic medications will have a larger impact on balance and gait when performed during a cognitive challenge task. This relationship will be investigated using serum anticholinergic activity (SAA) of blood to quantify medication burden.

Specific Aim 1: To determine whether the level of exposure to anticholinergic medications as measured by SAA affects standing balance and gait, thus increasing fall risk.

Hypothesis 1: Individuals with higher levels of SAA will experience impaired balance (increased sway and sway velocity) and gait (decreased gait speed and increased temporal variability) compared to individuals with lower levels of SAA.

Hypothesis 2: The impaired relationship of SAA level to balance and gait will be amplified when the balance and gait tasks are performed during a cognitive challenge task.

The second focus of this research project is to understand the impact of cerebrovascular disease on balance and gait. Specifically, cerebrovascular disease has been shown to affect processing speed and attention in older adults. This relationship will be investigated using quantified levels of cerebrovascular disease as defined by WMH on MRI.

Specific Aim 2: To determine whether the level of cerebrovascular disease (WMH) affects standing balance and gait, thus increasing fall risk.

Hypothesis 1: A decline in balance (increased sway and sway velocity) and gait (decreased gait speed and increased spatial variability) will be seen in individuals with higher levels of WMH.

Hypothesis 2: The relationship of WMH to negative effects on balance and gait will be enlarged when the balance and gait tasks are performed during a cognitive challenge task.

Finally, the third focus of this research project is to understand if the combination of anticholinergic burden and cerebrovascular disease in older adults will have an even greater impact on balance and gait. If SAA was linked to decrements in cognition and WMH has been linked to slower processing speed and decreased attention, it should be consistent that combining both detrimental variables should result in even more detrimental effects on balance and gait. This relationship will be assessed using WMH levels located in the neural tracts containing cholinergic fibers.

Specific Aim 3: To determine whether the level of combined effects of anticholinergic medications and WMH affect standing balance and gait, thus increasing fall risk.

Hypothesis 1: Individuals with higher levels of WMH in the cholinergic tracts will experience impaired balance (increased sway and sway velocity) and gait (decreased gait speed and increased temporal variability) compared to individuals with lower levels. The level of impairment will be greater than that seen in individuals with decrements only due to WMH or only due to SAA.

Hypothesis 2: The impaired relationship of WMH in the cholinergic tracts to balance and gait will be amplified when the balance and gait tasks are performed during a cognitive challenge task.

2.0 RESEARCH METHODS

2.1 ASSESSMENT OF SERUM ANTICHOLINERGIC ACTIVITY

To quantify the anticholinergic burden in the participants recruited for this study, 10 cc of blood from each participant were collected by a clinical phlebotomist at the Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania and analyzed to determine the individual serum anticholinergic activity (SAA). Quantification of SAA was done using a radioreceptor assay developed by Tune and Coyle (1981). Quinuclidinyl benzilate (^{3}H-QNB) binds specifically and with a high affinity to muscarinic cholinergic receptors. Anticholinergic drugs compete with ^{3}H-QNB at the receptor site as they are muscarinic inhibitors. With this, the ability of ^{3}H-QNB to bind to muscarinic receptors is reduced in proportion to the concentration of anticholinergic drugs in the blood serum collected. Using homogenized rat forebrain bound with ^{3}H-QNB, a 200 µL control serum without anticholinergic properties and added atropine was assayed to determine a standard curve for the amount of ^{3}H-QNB displaced for the specific neural tissue sample and amount of atropine used. Participant's SAA was expressed as the amount of atropine in a 1 mL sample of serum without anticholinergic properties that would be needed to inhibit the same amount of ^{3}H-QNB from binding to the muscarinic receptors of the rat forebrain as the participant's sample. The SAA level was expressed as pmole mL^{-1} of atropine equivalent serum. Using this method of reporting SAA, the serum levels of all anticholinergic drugs taken by

participants and unbound to proteins, including drug compounds, supplements, and their metabolites, could be quantified (Mulsant et al., 2003).

2.2 ASSESSMENT OF WHITE MATTER HYPERINTENSITIES

2.2.1 Magnetic Resonance Imaging

Each participant underwent magnetic resonance imaging (MRI) at the UPMC MR Research Center to quantify WMH. The scan was acquired using a Siemens 3 Tesla TIM TRIO scanner with eight channel coil (Siemens Medical Solutions USA, Inc., Malvern, PA). Axial series images along the transverse plane were acquired for each participant and included T1-weighted, fast spin-echo T2-weighted, fast fluid-attenuated inversion recovery (FLAIR), diffusion-tensor imaging, and magnetization-prepared rapid acquisition gradient-echo (MPRAGE).

2.2.2 Processing Magnetic Resonance Imaging Data

Analysis of all imaging data was conducted at the Geriatric Psychiatry Neuroimaging Lab under the supervision of Dr. Howard Aizenstein, M.D., Ph.D. Processing was performed using an automated method for segmenting and localizing WMH developed by Wu and colleagues (2006b). First, an intensity histogram of the FLAIR image was created to determine white matter, grey matter and cerebrospinal fluid. From this, WMH seeds were automatically generated. Using a fuzzy connected algorithm and individual parameters for each seed, WMH clusters containing the individual seeds were generated based on the fuzzy-connectedness or

affinity between voxels within the fuzzy object for the particular seed of interest. Upon generation of the individual WMH clusters from the identified seeds, the scattered WMH clusters were combined into final WMH segmentation volumes. Next, to localize the previously segmented WMH into regions of interest, an Automated Labeling Pathway (ALP) was employed. ALP was previously developed and has been used to automatically label specific anatomic regions of interest on structural MRI (Wu et al., 2006a). A high resolution reference image, the MNI colin27 image (MNI colin27), was registered to each participant's T1-weighted images using ALP. The T1-weighted images were preprocessed in order to match both the orientation and composition of the reference image. The Johns Hopkins University White Matter Atlas, which had been defined on the reference image, was then warped into each participant's registered image, creating anatomical definitions of individual regions within the brain image (Wakana et al., 2004). The T-1 image with landmarks was then masked onto the segmented FLAIR image so that areas defined as WMH were also given an anatomical point of reference.

2.2.3 Regions of Interest

A total of 20 individual tracts, as localized using the Johns Hopkins University White Matter Atlas, were defined for each image along with the sum of these tracts (WMH ALL) and total white matter volume. The total white matter volume was significantly correlated with WMH ALL with a Pearson correlation coefficient of 0.93 and p-value <0.0001. With such a high correlation, only WMH ALL was selected for the analysis. Individual tracts were also identified as either containing (CHOL) or not containing cholinergic fibers (NON-CHOL). Since anticholinergic burden and its interaction with WMH in the participants of this work are of importance, these measures may allow quantification of this interaction. In addition to overall

WMH and cholinergic tracts, the analysis also utilized eight of the specific tracts, combined into three variables of interest. The sum of the left and right anterior thalamic radiation and the left and right corticospinal tract was defined as AACC. The left and right superior longitudinal fasciculus were summed and defined as SS. The frontal and occipital regions of the corpus callosum were also summed and defined as CC. The tracts the their combinations selected for analysis were based on previous research linking the importance of the tract to either or a combination of motor function, cognition and processing, and executive function (Sheline et al., 2008; Sparto et al., 2008; Duering et al., 2011). Quantification of WMH was done using a normalized voxel count in which the number of voxels containing WMH in the region of interest was divided by the total brain volume, yielding a percentage of total brain volume.

2.3 COGNITIVE TASK

2.3.1 Determining Cognitive Task Difficulty

Half of all balance and gait trials were conducted under a cognitive dual-task condition. The chosen task, digit recall, was challenging, adjustable to individual cognitive capacity, and provided by an auditory stimulus. This task has been previously used in older adults and was shown to make a major demand on participants' working memory (Nebes et al., 2001). Each participant was first assessed at the Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania by one of the study's co-investigators to determine participant-specific digit spans. Starting with two digits, a list of numbers was presented at a rate of one digit per second, and the participant was asked to recall them in the reverse order. For example, if the participant was

given ***1, 4***, they would repeat back "***4, 1***". The participant received two lists of numbers of the same length. The number of digits was increased by one if the participant could correctly repeat one of the two lists in the previous series. This was continued until the participant could not correctly repeat back either of the lists within a series or the participant was successful with a string of eight digits. The participant's digit span for the testing duration was set at the longest number of digits that could be correctly recalled for at least one of the two lists given. This span was between two and eight digits.

2.3.2 Cognitive Challenge Task during Data Collection

During both standing balance and gait trials, participants experienced one of three cognitive conditions. The first, no task (NT), was a control task in which participants did not receive an auditory stimulus. The second, forward (F), was a cognitive challenge task in which participants were asked to repeat the list of words presented to them in the same order in which they were received. For example, if the participant was given ***1,5,7,8*** followed by the word ***repeat***, the participant would respond ***"1,5,7,8"***. The third task, backwards (B), was a cognitive challenge task in which participants were asked to repeat the list of words presented to them in the opposite order in which they were received. For example, if the participant was given ***2,5,6,9*** followed by the word ***backward***, the participant would respond ***"9,6,5,2"***. The number of digits presented to each participant was based on the previous screening as described above and remained constant for all trials. Using Logitech ClearChat PC Wireless headphones (A-00007, Logitech, Fremont, CA), the auditory stimulus was provided into the headset and participant responses were recorded using the attached microphone. All balance and gait trials were conducted in groups of three. With this, the order of cognitive conditions remained constant for each participant. The

first trial of each group was always NT. The second and third were randomized such that it was either F then B or B then F. The order of the second and third trials remained consistent for the entire testing session.

2.3.3 Cognitive Task Performance Scoring

Performance on the cognitive task was scored at the conclusion of the balance and gait assessments at the Western Psychiatric Institute and Clinic. Scoring was based on a system allowing partial credit for correctly recalling certain portions of the list. Digits recalled were counted as correct if: the first or last digit of a string was correctly recalled, any correct digits adjacent to a correctly recalled first or last digit was recalled, and any correct sequence of three or more digits anywhere in the response was recalled (Drachman & Zaks, 1967). For example, if the list given was 1,2,3,5,7,9 and the participant was to repeat it backwards, the participant would receive a score of six out of six for this list if 9,7,5,3,2,1 was repeated. If 9,7,3,5,2,1 was repeated, the participant would receive a point for the 9, 7, 2 and 1, giving a score of four out of six. Finally, if 9,8,7,5,3,1 or 9,7,7,5,3,1 was repeated, the participant would receive a score of three out of six. For each scenario, the 9, 7, 5, 3 and 1 are correct. The group of 7 5 3 forms a correct sequence of three digits. However rather than scoring four out of six, one point is deducted from each score because an intrusion, or a digit that is not part of the series, is inserted into the first scenario, and a number is repeated in the second scenario. The number of correct digits is averaged over the number of digits presented in 60 seconds. This number is then divided by the participant's specific digit span and documented as a percent correct for that task. For example, a participant averaged 3.2 digits correct over 60 seconds with a digit span of 5. For that trial, the participant's cognitive task accuracy would be 64%. The accuracy score was then

normalized to a seated accuracy score by subtracting the accuracy of performance during the specific trial of interest from the accuracy of a seated baseline trial conducted prior to testing.

2.4 EQUIPMENT

2.4.1 Testing Area

All data to perform the postural and gait analyses were collected in the Human Movement and Balance Laboratory located at the University of Pittsburgh, Pittsburgh, Pennsylvania (Figure 1). The laboratory was equipped with two embedded Bertec force plates (4060A, Bertec, Inc., Columbus, OH) and a Vicon 612 motion capture system. Eight IR M2-cameras (Vicon, Centennial, CO) captured motion data at 120 Hz while analog signals from the forceplates were recorded at 240 Hz from a 12-bit National Instruments A/D converter.

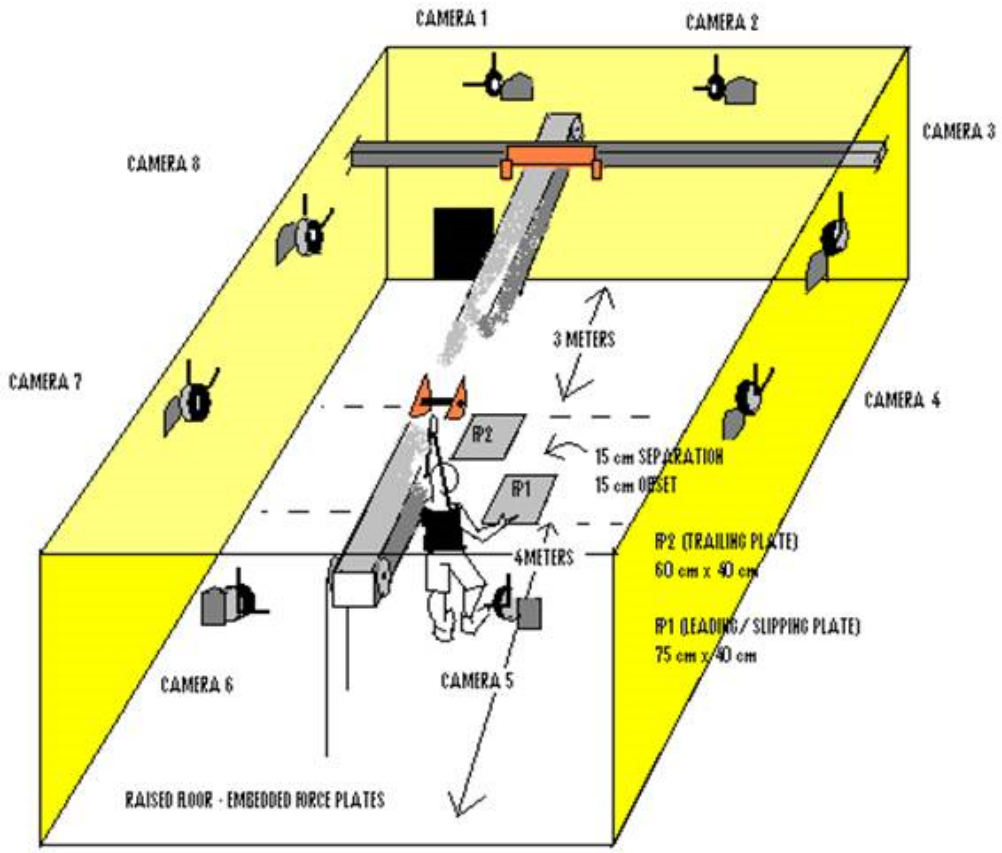

Figure 1: Schematic depicting laboratory layout. Eight Vicon motion capture cameras shown around room with embedded forceplates indicated by rectangles labeled P1 and P2.

2.4.2 Motion Capture Set-up

Using the Vicon 612 motion capture system and Vicon Workstation, three dimensional trajectories were collected and reconstructed for all standing balance and gait trials. For standing trials, participants were instrumented with a custom marker set including 14 reflective markers. During gait trials, an additional 12 reflective markers were added to the feet, generating 26 trajectories (Figure 2 and Figure 3). All segments were considered rigid bodies for analysis purposes.

Figure 2: Motion capture marker placement on the anterior (left) and posterior (right) pelvis and upper body. The sternum marker, used for gait speed, is indicated by the red circle.

Figure 3: Anterior (left), lateral (middle), and medial (right) views of motion capture marker placement on polyvinyl soled shoes for testing. A total of nine markers were used on each foot including one on the lateral malleolus (not shown).

2.4.3 Footswitches

Participants' shoes were instrumented with custom on-off membrane footswitches for all gait trials. These switches were used to temporally identify heel contact and toe off events during gait. On the sole of the shoe, the toe switch was placed on the anteriomedial edge, and the heel switch was placed on the posteriolateral edge (Figure 4). Switches were rated for five ounce activation. Analog voltages were collected and digitized using a BluSentry Bluetooth Adapter (RN-800S-CB, Roving Networks, Los Gatos, CA) mounted in an electronics enclosure worn on the waistband. The digitized signals were then transmitted wirelessly to a paired Bluetooth receiver (TBW 104UB Version 2.1R, TRENDNET, Torrance, CA) at 120 Hz.

Figure 4: Polyvinyl soled shoe instrumented with two simple on-off membrane switches for temporal heel contact and toe off events.

2.5 PARTICIPANTS

A total of 48 older adults (27 females, 21 males) were recruited to participate in this study (Table 1). Written informed consent was obtained prior to participation and approved by the University of Pittsburgh Institutional Review Board. Participants were screened for neurological, visual, orthopedic, cardiovascular, medication use, and any other physical abnormalities that would prevent them from standing with their feet together or affect their balance or gait. All participants were asked to wear comfortable clothing with a shirt that could be tucked in. Additionally, participants were outfitted with the same polyvinyl, flat soled shoe to maintain consistency in equipment used to obtain footswitch data.

Table 1: All participant characteristics including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.6 (4.05) [70.3-83.5]	1.68 (0.09) [1.52-1.87]	75.9 (14.7) [47.4-119.6]

2.6 STANDING BALANCE ASSESSMENT

2.6.1 Standing Balance Protocol

Each participant underwent 12 trials in the standing balance protocol. For the first six trials, participants were instructed to stand on the right embedded forceplate with their eyes open (EO), feet side-by-side and completely touching, and remain still for 60 seconds. As described previously, the first trial was NT while the second and third were randomized to F then B or B then F. This same order of trials was repeated for trials four through six. For the second half of the 12 trials, participants were instructed to stand on the right embedded forceplate with their eyes closed (EC) feet side-by-side and completely touching, and remain still for 60 seconds. The cognitive conditions were repeated in the same order as done in the previous trials with EO.

2.6.2 Standing Balance Analysis

While all 48 participants completed the standing balance protocol, a subset of 40 participants was selected for analysis (Table 2) due to availability of SAA and WMH data. Of these 40, all were included in the analysis with SAA, 36 were included in the analysis with WMH ALL and

the individual WMH tracts (Table 3), and 21 were included in the analysis with CHOL and NON-CHOL (Table 4).

Table 2: Standing balance participant characteristics for overall analysis and analysis of SAA (n=40) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.6 (4.06) [70.3-83.5]	1.69 (0.09) [1.53-1.87]	75.9 (14.9) [47.4-119.6]

Table 3: Standing balance participant characteristics for analysis of WMH ALL and individual WMH Tracts (n=36) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.2 (3.95) [70.6-83.4]	1.69 (0.08) [1.53-1.87]	76.2 (12.5) [55.6-107.5]

Table 4: Standing balance participant characteristics for analysis of CHOL and NON-CHOL tracts (n=21) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
74.6 (3.42) [70.6-83.3]	1.69 (0.08) [1.53-1.87]	75.4 (12.8) [55.6-102]

The raw digital output collected by the forceplate was imported into MATLAB (R2010a, MathWorks, Natick, MA) for all analyses. Center of pressure in the medial-lateral (ML) direction (COP_{ML}) and center of pressure in the anterior-posterior (AP) direction (COP_{AP}) were first calculated over the entire trial from the raw data using the following formulas:

$$COP_{ML} = \frac{(-H \times F_X(i) - M_Y(i))}{F_Z(i)} \qquad COP_{AP} = \frac{(-H \times F_Y(i) - M_X(i))}{F_Z(i)}$$

In these formulas, i is the individual frame number, H is the height difference from the floor surface to the forceplate, F_X is the force in the x-direction, F_Y is the force in the y-direction, F_Z is the force in the z-direction, and M_Y is the moment generated about the y-axis. Center of pressure in each direction was zero meaned by subtracting the average center of pressure for the entire trial from the center of pressure at each point in time. The zero meaned data was filtered using an eighth order Butterworth filter with cut-off frequency of 1.5 Hz and downsampled to 120 Hz.

The standard deviations of both COP_{ML} and COP_{AP} (ML RMS and AP RMS, respectively) were calculated using the following formulas (Maurer & Peterka, 2005):

$$ML\ RMS = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(COP_{ML}(i) - \overline{COP_{ML}})^2} \qquad AP\ RMS = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(COP_{AP}(i) - \overline{COP_{AP}})^2}$$

The mean sway velocity of both COP_{ML} and COP_{AP} (ML VEL and AP VEL, respectively) were calculated using the following formulas (Maurer & Peterka, 2005):

$$ML\ VEL = \frac{1}{n-1}\sum_{i=1}^{n-1}|COP_{ML}(i+1) - COP_{ML}(i) \times 120|$$

$$AP\ VEL = \frac{1}{n-1}\sum_{i=1}^{n-1}|COP_{AP}(i+1) - COP_{AP}(i) \times 120|$$

Finally, the distance covered by the center of pressure in both directions or the total change in resultant center of pressure (PL) was calculated and time normalized using the following formula (Kim et al., 2009):

$$PL = \sum \sqrt{(COP_{ML}(i+1) - COP_{ML}(i))^2 + (COP_{AP}(i+1) - COP_{AP}(i))^2} \times \frac{120}{n}$$

Only the second trial within each condition was used for analysis in order to eliminate any practice effects seen in the first trial. The statistical analysis consisted of two parts. First, we determined the effect of eye and task conditions on standing balance by fitting a mixed linear model. The analysis was done using subject as a random effect and fixed effects of eye condition, task condition, and the interaction of the two. The dependent variables included AP RMS, ML RMS, PL, AP VEL, and ML VEL and were each considered individually. Statistical significance was set at 0.05. Graphically, the relationship of the balance outcome measures and predictor variables SAA, WMH ALL, AACC, CC, and SS appeared non-linear. The second analysis was performed to explore this non-linear relationship between the outcome balance measures and the predictor variables. We computed the Spearman rank correlation coefficient (ρ) within each task and eye condition between each standing balance variable and the predictor

variables. The dependent variables were AP RMS, ML RMS, PL, AP VEL, and ML VEL. The independent variables were SAA, WMH ALL, AACC, CC, SS, CHOL, and NON-CHOL. Statistical significance was again set at 0.05. This correlation analysis was repeated with the addition of average gait speed from the NT gait trial from each subject as a controlling variable to obtain partial correlation coefficients. With this addition, the analysis was done to look at the relationship of the balance outcome measures to the predictor variables while controlling for gait speed. This can be interpreted as controlling for overall health status. Statistical significance remained at 0.05. All statistical analyses were conducted using SAS® version 9.2 (SAS Institute Inc., Cary, NC).

2.7 GAIT ASSESSMENT

2.7.1 Gait Protocol

Each participant underwent six gait trials. Participants were asked to walk at a self-selected pace around an outlined oval-shaped track for 60 seconds with their eyes open (Figure 5). Participants averaged 5 complete laps around the track. With regards to cognitive tasks, the first trial was NT while the second and third were randomized to F then B or B then F. This same order of trials was repeated for trials four through six. Footswitch and Vicon motion capture data were collected during the entire trial; however, the data captured only over the straightaways were processed. It was assumed that after elimination of the curves from the data that the participant was considered to be continuously walking and that data from the individual passes could be merged into one larger trial for analysis.

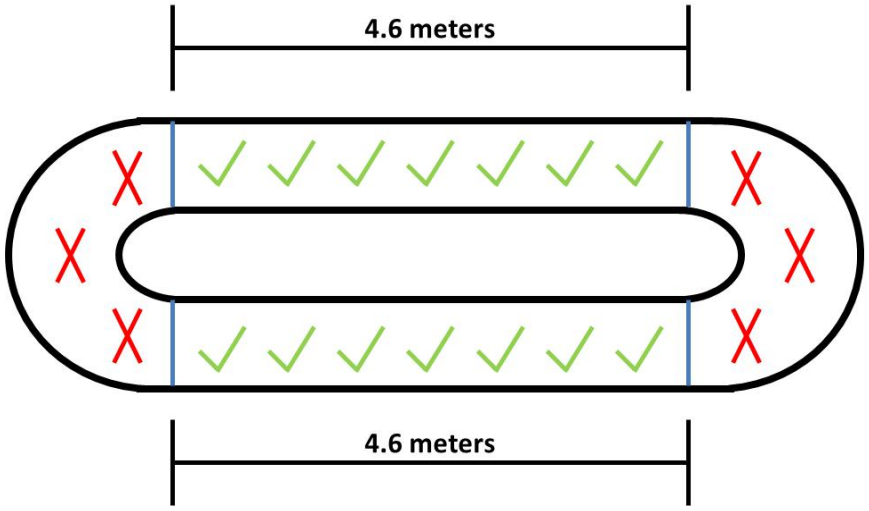

Figure 5: Circular track set-up and distance traveled for each straightaway. Only data collected on the straightaways (indicated by green check marks) were processed.

2.7.2 Gait Analysis

While all 48 participants completed the gait protocol, a subset of 41 participants was selected for analysis (Table 5) due to the availability of SAA and WMH data. Of these 41, 40 were included in the analysis with SAA (Table 6), 34 were included in the analysis with WMH ALL and the individual WMH tracts (Table 7), and 20 were included in the analysis with CHOL and NON-CHOL (Table 8).

Table 5: Gait participant characteristics for overall analysis (n=41) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.5 (3.89) [70.6-83.5]	1.68 (0.091) [1.52-1.87]	76.9 (14.8) [47.4-119.6]

Table 6: Gait participant characteristics for analysis of SAA (n=40) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.6 (3.89) [70.3-83.5]	1.68 (0.09) [1.52-1.87]	76.2 (15.1) [47.4-119.6]

Table 7: Gait participant characteristics for analysis of WMH ALL and individual WMH tracts (n=34) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.2 (3.7) [70.6-83.4]	1.67 (0.09) [1.52-1.87]	76.7 (12.2) [55.6-107.5]

Table 8: Gait participant characteristics for analysis of CHOL and NON-CHOL tracts (n=20) including mean, (SD), [range]

Age [years]	Height [m]	Weight [kg]
75.4 (3.52) [70.6-83.3]	1.67 (0.09) [1.52-1.87]	75.5 (12.7) [55.6-102]

Using the Vicon motion capture video output, frame ranges were identified as to when the participant was walking across the straightaways of the track so that marker and footswitch data were analyzed only over those particular frames. One straightaway frame range was referred to as one pass. For each pass, the sternum marker was identified and labeled from the reconstructed trajectories from the Vicon motion capture data. The trajectory of the sternum in the Y direction (STRNY) was then exported to calculate gait speed in MATLAB. The raw digital footswitch signal collected by the Bluetooth receiver was imported into MATLAB. Using a custom MATLAB code, heel contact and toe off were temporally identified over the designated frame ranges for each pass. Heel contact was identified as the temporal location of the rising edge of the right and left heel switch voltages. Toe off was identified as the temporal location of the falling edge of the right and left toe switch voltages (Figure 6).

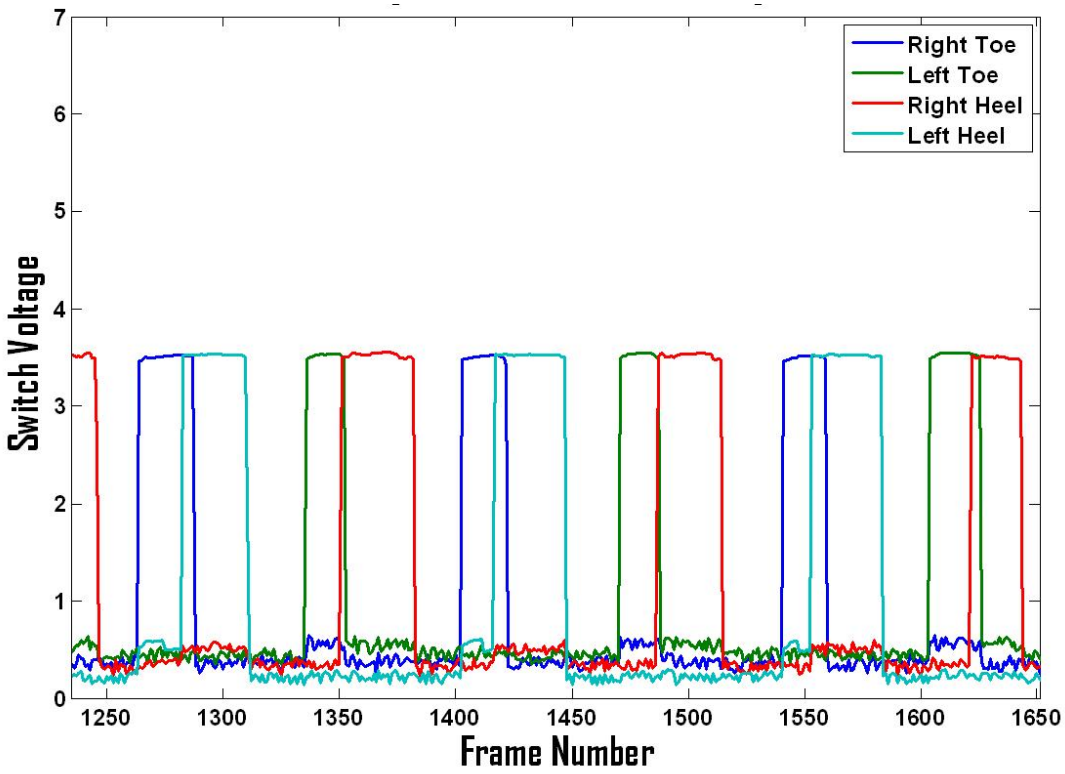

Figure 6: Typical output for one pass showing both left and right heel and toe switches. Heel contact is identified as the rising edge of the voltage from the heel switch. Toe off is identified as the falling edge of the voltage from the toe switch.

Using MATLAB, gait speed (GS), or the velocity in the direction of travel, was calculated. For each pass, continuous gait speed was calculated over the entire duration using the following formula:

$$GS = STRNY(i+1) - STRNY(i) \times 120$$

Using an interclass correlation (ICC) on a sub-set of average gait speeds from 10 participants with 12 passes, it was statistically demonstrated that after the first six passes, gait

speed stabilized and the ICC was 0.90. With this, the average gait speed (Average GS) for each participant for each trial type was defined as the average gait speed over the first six passes per trial.

The standard deviation of several temporal gait parameters was calculated across all passes for each trial using the heel contact and toe off values determined from the footswitch data. These variables included stance time variability in milliseconds (STV), double support time variability in milliseconds (DSV), step time variability in milliseconds (SEV), and cadence variability in steps per minute (CV). Stance time was defined as the time from heel contact to toe off of the same foot or the time spent with each foot completely on the ground. Double support time was defined as the time from toe off of one foot to the next heel contact of the other foot or the time spent when both feet are on the ground. Step time was defined as the time from heel contact of one foot to the next heel contact of the other foot or the time between stepping with one foot and stepping with the next. Cadence was defined as the number of steps taken per minute. The variables were calculated for both the left and right feet and averaged across both sides under the assumption that gait was symmetrical.

As in the statistical analysis for standing balance, only the second trial within each condition was used to eliminate any practice effects seen in the first trial. The statistical analysis consisted of three parts. First, we determined the effect of task conditions on temporal variability by fitting a linear mixed model. The analysis was done using subject as a random effect and task condition as a fixed effect. The dependent variables included Average GS, STV, DSV, SEV, and CAD and were each considered individually. Statistical significance was set at 0.05. Graphically, the relationship of the temporal variability measures and predictor variables SAA, WMH ALL, AACC, CC, and SS appeared linear. The second analysis was used to explore this linear

relationship between the temporal variability measures and the predictor variables. We computed the Pearson correlation coefficient (r) within each task between each temporal variability measure and the predictor variables. The dependent variables were Average GS, STV, DSV, SEV and CAD. The independent variables were SAA, WMH ALL, AACC, CC, SS, CHOL, and NON-CHOL. Statistical significance was again set at 0.05. This correlation analysis was run a second time but with the addition of average gait speed from each gait trial from each subject as a partial correlation variable. With this addition, the analysis was done to look at the relationship of the temporal variability measures to the predictor variables while controlling for gait speed. This can be interpreted as controlling for overall health status. Statistical significance remained set at 0.05. Since we were controlling for gait speed, this analysis was not conducted on average GS.

The final analysis was conducted to determine the proportion of variability in the temporal variability measures explained by the predictor variables in addition to that explained by average GS within each task. First, temporal variability measures were regressed on average GS and each predictor variable individually and then simultaneously in different regression models. Each model's R^2 was then examined to quantify the average GS contributions alone (A), each predictor variable's contribution alone (B), and the simultaneous contribution of average GS and each predictor variable (C). By calculating the difference between model A and C (C-A), the added value of each predictor variable to explaining the variability in temporal variability above and beyond that by average GS was determined. To determine the statistical significance of the R^2 difference, a nested models F-test was performed. Statistical significance was held at 0.05. All statistical analyses were conducted using SAS® version 9.2 (SAS Institute Inc., Cary, NC).

3.0 RESULTS

3.1 STANDING BALANCE

3.1.1 Characteristics of Independent Predictor Variables

Within the overall standing balance analysis, three different analysis groups were defined to include SAA, CHOL and NON-CHOL, and WMH. Table 9 provides the summary statistics of each independent variable of interest to better understand the dataset used for analysis. All variables pertaining to WM are shown as percentages of total brain volume.

Table 9: Summary statistics for independent variables used in standing balance analysis

Independent Variable [units]	Mean	SD	Range
SAA [pmole mL atropine equivalent^{-1}]	0.54	0.61	0-2.05
CHOL [% Total Brain Volume]	0.000656	0.000615	0-0.00177
NON-CHOL [% Total Brain Volume]	0.00999	0.0109	0.000251-0.0320
WMH ALL [% Total Brain Volume]	0.104	0.0974	0.00219-0.542
AACC [% Total Brain Volume]	0.0582	0.0466	0-0.215
CC [% Total Brain Volume]	0.0362	0.0332	0-0.135
SS [% Total Brain Volume]	0.00342	0.000861	0-0.0595

3.1.2 Effect of Vision and Dual-Task on Standing Balance

The effect of standing with both EO and EC was investigated for all subjects within each analysis group through the use of a mixed linear regression model. As expected, eye condition was significant across all subjects with $p<0.0001$ for all COP variables of interest. In addition to eye condition, the effect of performing a dual-task while standing was also investigated, and surprisingly, task effects were only revealed in five of the fifteen dependent variables analyzed. The interaction effect of eye and task condition did not reveal any significance. The p-values for all effects and results of the post-hoc analysis for the task effect are presented in Table 10 with statistical significance indicated by an asterisk.

Table 10: Statistical analysis of all dependent COP variables to determine task and eye condition effects. p-values are provided (α=0.05). Significance is denoted by an asterisk (*).

COP Variable	Analysis Group	Eye Condition	Task	Task Post-hoc	Interaction
AP RMS	SAA	<0.0001 *	0.011 *	NT/F	0.54
ML RMS	SAA	<0.0001 *	0.15		0.82
PL	SAA	<0.0001 *	0.049 *	NT/B	0.57
AP VEL	SAA	<0.0001 *	0.025	NT/B	0.55
ML VEL	SAA	<0.0001 *	0.23		0.67
AP RMS	CHOL/NON-CHOL	<0.0001 *	0.025 *	NT/F	0.37
ML RMS	CHOL/NON-CHOL	<0.0001 *	0.058		0.92
PL	CHOL/NON-CHOL	<0.0001 *	0.54		0.33
AP VEL	CHOL/ NON-CHOL	<0.0001 *	0.12		0.55
ML VEL	CHOL/ NON-CHOL	<0.0001 *	0.81		0.31
AP RMS	WMH	<0.0001 *	0.064		0.45
ML RMS	WMH	<0.0001 *	0.36		0.74
PL	WMH	<0.0001 *	0.083		0.34
AP VEL	WMH	<0.0001 *	0.043 *	NT/B	0.51
ML VEL	WMH	<0.0001 *	0.26		0.29

These effects are further demonstrated graphically in Figures 7, 8, and 9. Across all analyses, the dependent variables of interest increase significantly when participants stand with EC compared to EO.

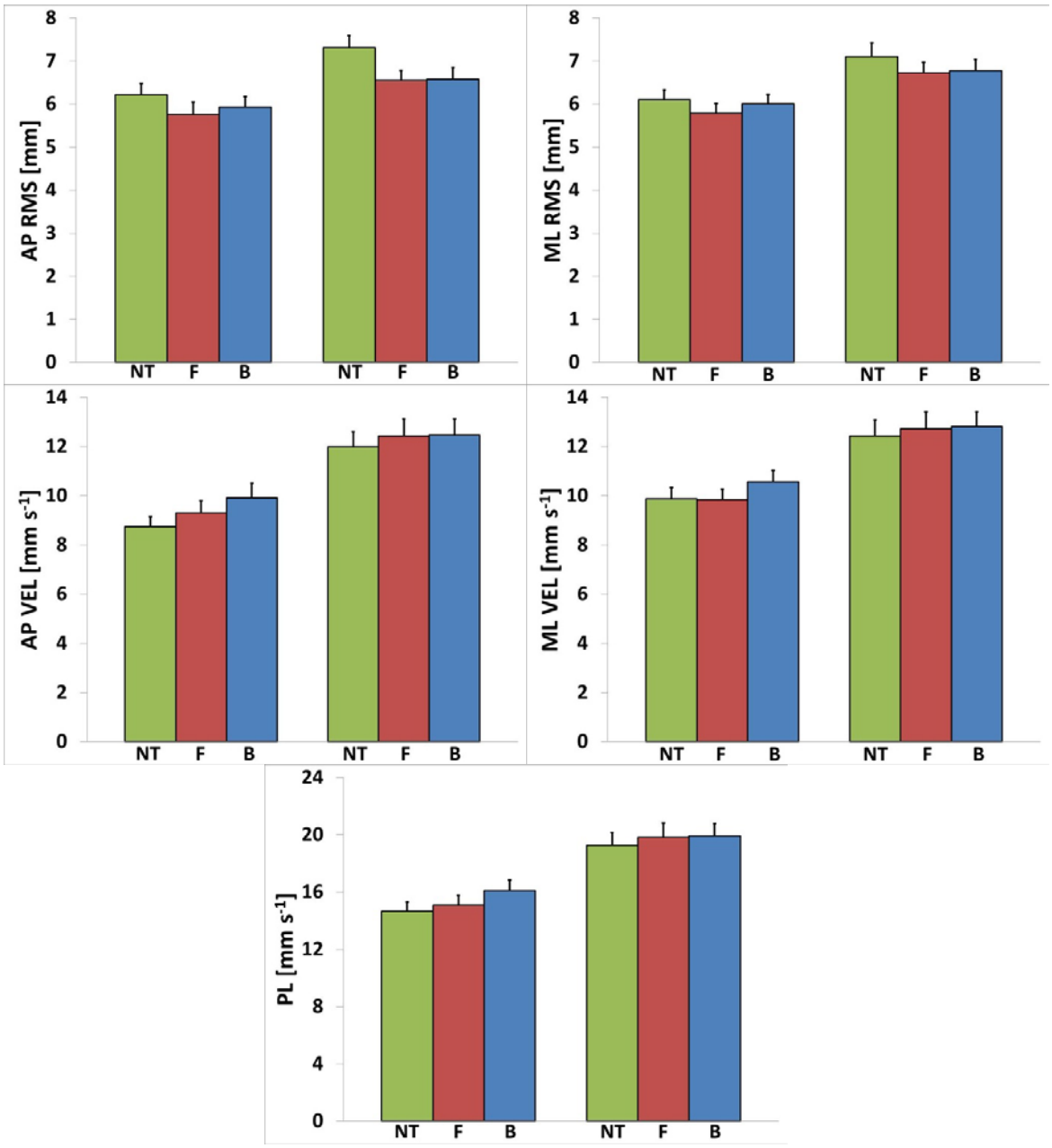

Figure 7: Averaged COP variables across each task for EO and EC for SAA cohort. EO is represented by the three bars on the left while EC is represented by the three bars on the right. Eye condition was significant for all variables of interest. Standard error bars are shown.

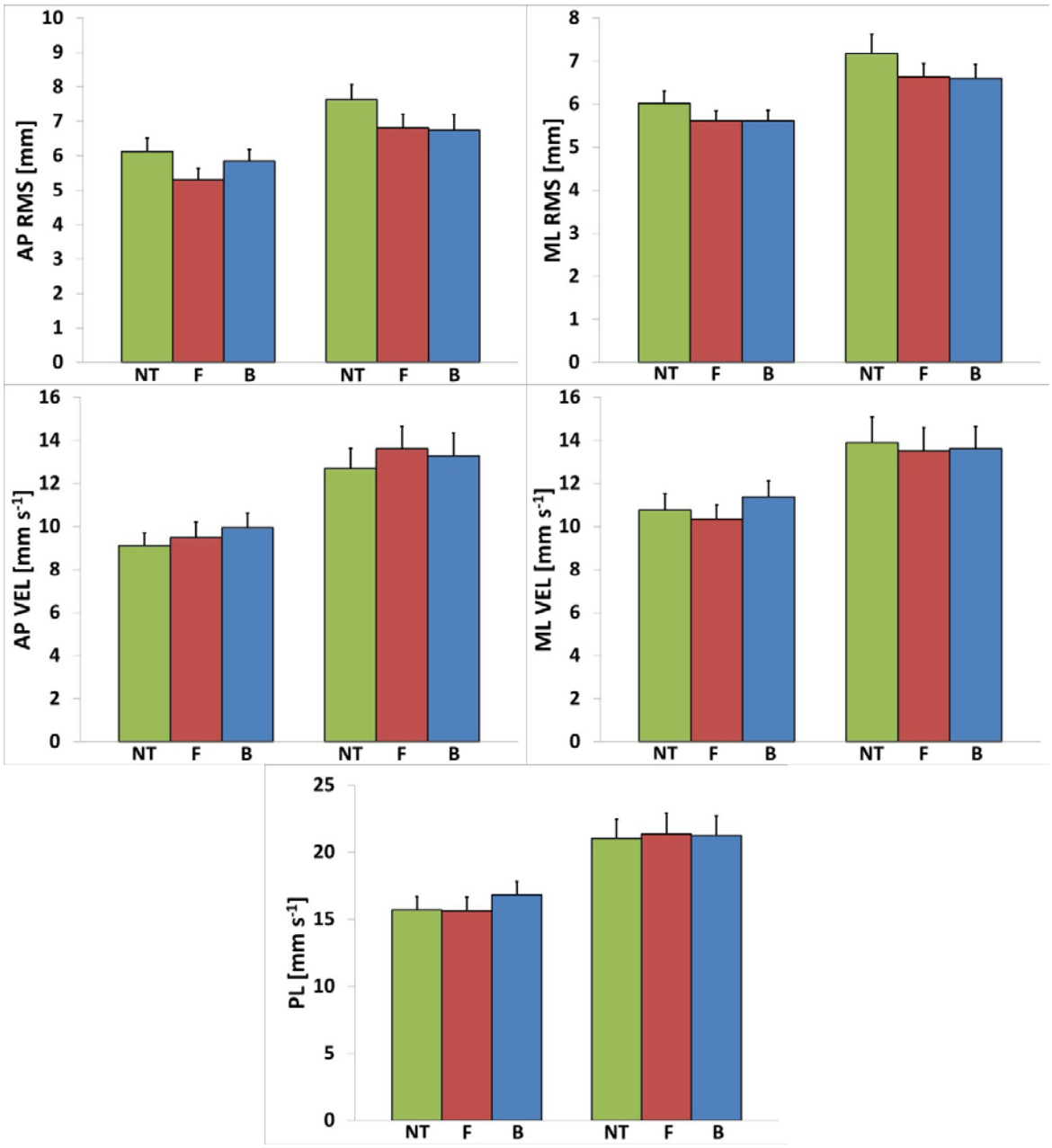

Figure 8: Averaged COP variables across each task for EO and EC for CHOL and NON-CHOL cohort. EO is represented by the three bars on the left while EC is represented by the three bars on the right. Eye condition was significant for all variables of interest. Standard error bars are shown.

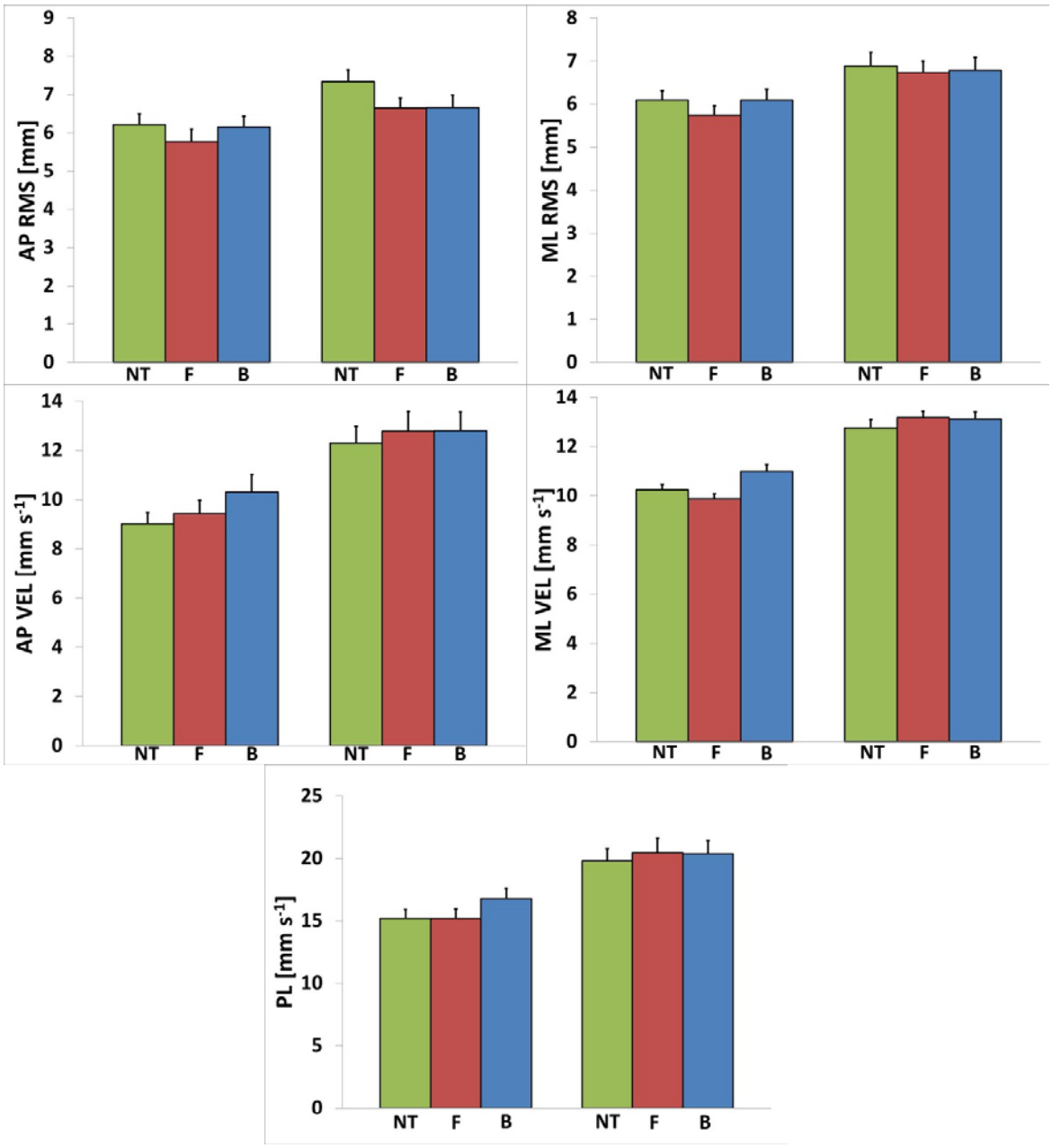

Figure 9: Averaged COP variables across each task for EO and EC for WMH ALL and individual tract cohort. EO is represented by the three bars on the left while EC is represented by the three bars on the right. Eye condition was significant for all variables of interest. Standard error bars are shown.

3.1.3 Standing Balance and SAA

Using the Spearman correlation coefficient, the non-linear relationship between the outcome balance measures and SAA was examined. This was done across all three tasks and both eye conditions. There were no significant relationships between these variables. The Spearman coefficients and corresponding p-values are presented in the appendix, Table 17. The same relationship between the COP variables of interest and SAA was reanalyzed to better understand if the differences in balance outcome measures were due to overall health. This was done by adjusting for gait speed within the statistical model. The average GS during the first NT gait trial was used. Again, there were no significant relationships between these variables. The adjusted Spearman rank correlation coefficients and their corresponding p-values are presented in the appendix, Table 17.

3.1.4 Standing Balance and WMH

The Spearman rank correlation coefficient was again utilized to describe the relationship between the outcome balance variables of interest and WMH ALL, AACC, CC, and SS. Significant relationships were seen when participants did not perform a dual-task and had their eyes closed. With EC, significant relationships existed between standing balance and WMH ALL, AACC and CC. There were no significant relationships during any of the tasks with EO or F or B dual-task conditions with EC. The Spearman correlation coefficients for the NT condition under EC for select predictor variables and balance outcome measures are shown in Table 11. All Spearman correlation coefficients are presented in the appendix, Table 17. A positive

correlation coefficient indicates an increase in the balance sway measure with an increase in the predictor variable. All significant findings demonstrated this relationship.

Table 11: Unadjusted Spearman rank correlation coefficients and their corresponding p-values describing the relationship between the COP variables of interest and WMH ALL, AACC, and CC (α=0.05) for EC conditions without a dual-task. Significance is denoted by an asterisk (*).

COP Variable	Predictor Variable	Eye Condition	Task Condition	Spearman Coefficient	p-value
AP RMS	AACC	EC	NT	0.23	0.18
ML RMS	AACC	EC	NT	0.34	0.045 *
ML VEL	AACC	EC	NT	0.17	0.31
AP RMS	CC	EC	NT	0.19	0.27
ML RMS	CC	EC	NT	0.45	0.0057 *
ML VEL	CC	EC	NT	0.38	0.022 *

The same relationship between the COP variables of interest and WMH ALL, AACC, CC, and SS was reanalyzed to investigate if the differences in balance outcome measures were attributed to overall health by adjusting for gait speed within the statistical model. There were significant relationships seen in both eye conditions when not performing a task. Additionally, significant relationships were also seen when participants stood with their eyes closed with F task. The Spearman correlation coefficients for the NT condition under both EO and EC and for the F condition under EC for select predictor variables and outcome measures are shown in Table 12. All adjusted Spearman correlation coefficients are presented in the appendix, Table 17. Again, all significant findings demonstrated a positive relationship.

Table 12: Adjusted Spearman rank correlation coefficients and their corresponding p-values describing the relationship between the COP variables of interest and WMH ALL, AACC, SS, and CC (α=0.05) for EC and EO conditions without a dual-task and EC with a F task. Significance is denoted by an asterisk (*).

COP Variable	Predictor Variable	Eye Condition	Task Condition	Spearman Coefficient	p-value
AP RMS	WMH ALL	EC	NT	0.36	0.0337 *
ML RMS	WMH ALL	EC	NT	0.45	0.0063 *
ML VEL	WMH ALL	EC	NT	0.29	0.085
AP RMS	AACC	EC	NT	0.24	0.18
ML RMS	AACC	EC	NT	0.39	0.022 *
ML VEL	AACC	EC	NT	0.23	0.20
AP RMS	CC	EC	NT	0.22	0.21
ML RMS	CC	EC	NT	0.51	0.0023 *
ML VEL	CC	EC	NT	0.44	0.012 *
AP RMS	SS	EC	NT	0.46	0.0061 *
ML RMS	SS	EC	NT	0.23	0.19
ML VEL	SS	EC	NT	0.269	0.12
AP RMS	WMH ALL	EC	F	0.37	0.031 *
ML RMS	WMH ALL	EC	F	0.16	0.35
ML VEL	WMH ALL	EC	F	0.16	0.35
AP RMS	CC	EC	F	0.39	0.023 *
ML RMS	CC	EC	F	0.27	0.12
ML VEL	CC	EC	F	0.28	0.10
AP RMS	SS	EC	F	0.29	0.086
ML RMS	SS	EC	F	0.35	0.041 *
ML VEL	SS	EC	F	0.21	0.23
AP RMS	CC	EO	NT	0.38	0.026 *
ML RMS	CC	EO	NT	0.22	0.21
ML VEL	CC	EO	NT	0.35	0.041 *

Figures 10-13 further demonstrate the significant relationships between two of the balance measures and the corresponding predictor variables.

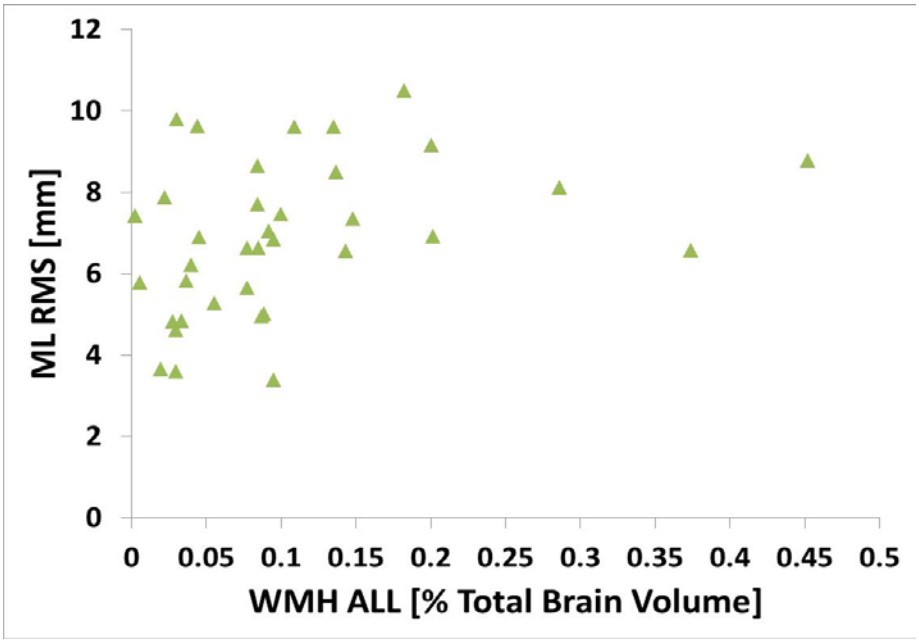

Figure 10: ML RMS [mm] vs. WMH ALL [% Total Brain Volume] under the NT, EC condition. The relationship between these two variables is significant with a Spearman rank correlation coefficient of 0.45 and p=0.0063. With a positive correlation, as the overall WMH for all tracts increases, ML RMS also increases.

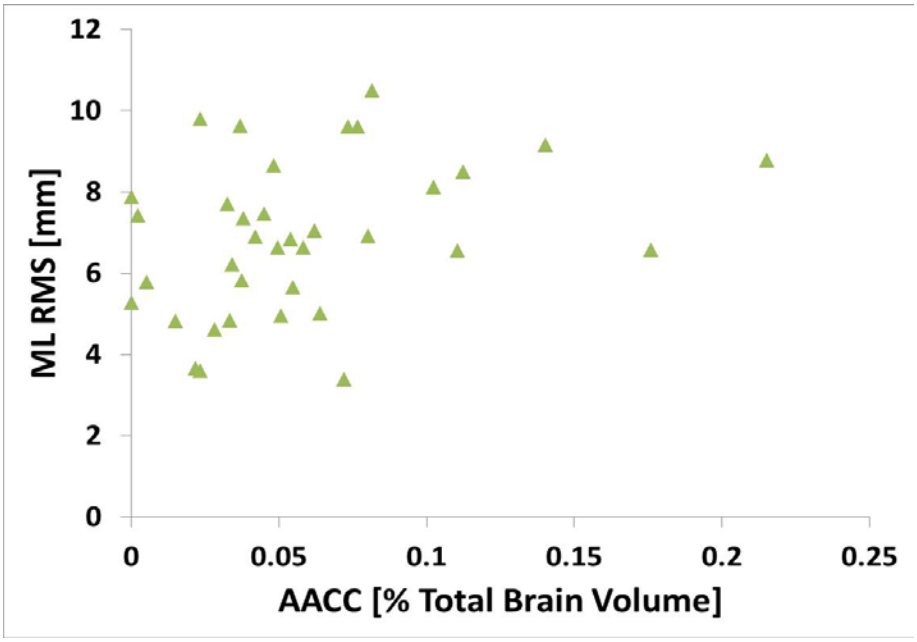

Figure 11: ML RMS [mm] vs. AACC [% Total Brain Volume] under the NT, EC condition. The relationship between these two variables is significant with a Spearman rank correlation coefficient of 0.39 and p=0.022. With a positive correlation, as AACC increases, ML RMS also increases.

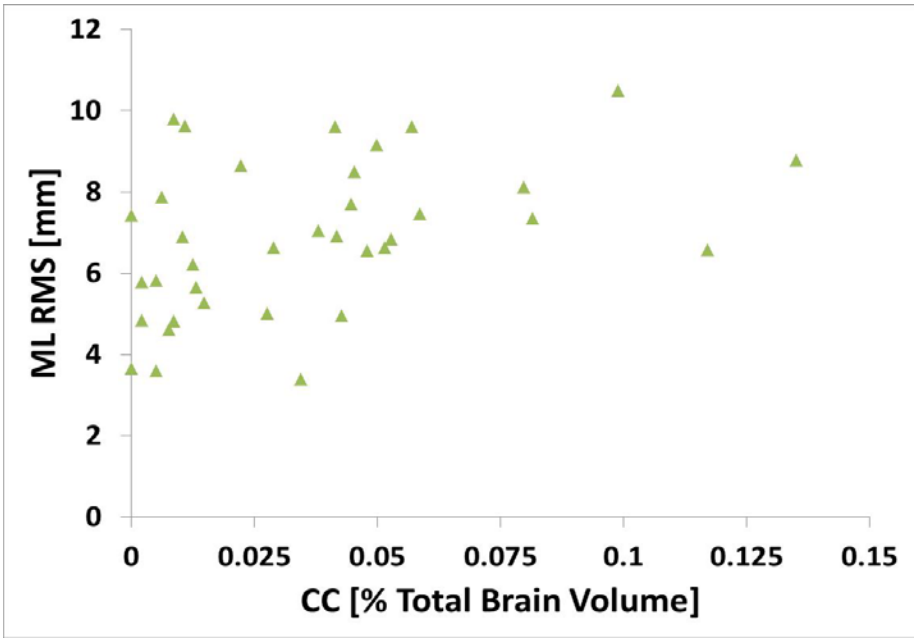

Figure 12: ML RMS [mm] vs. CC [% Total Brain Volume] under the NT, EC condition. The relationship between these two variables is significant with a Spearman rank correlation coefficient of 0.51 and p=0.0023. With a positive correlation, as CC increases, ML RMS also increases.

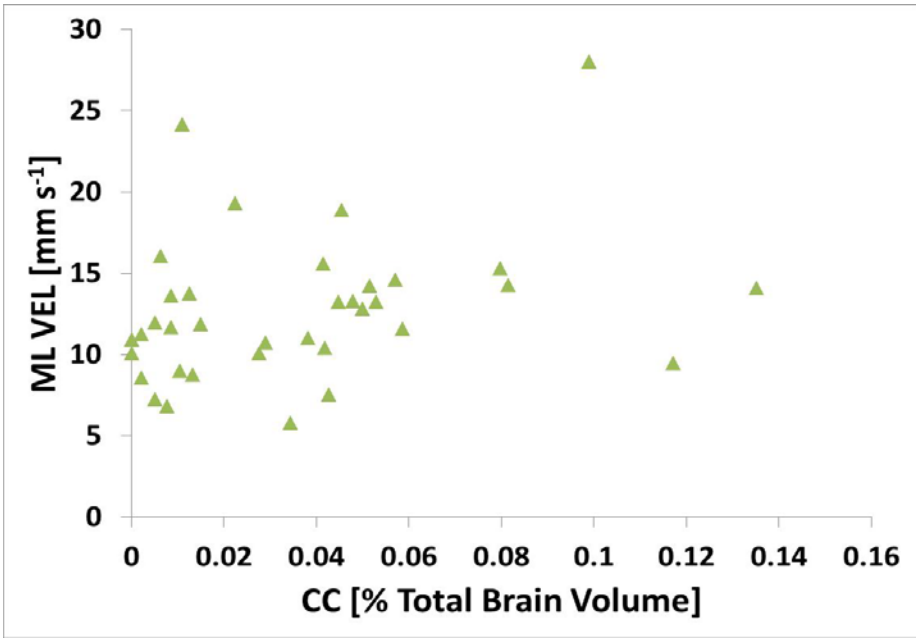

Figure 13: ML VEL [mm s^{-1}] vs. CC [% Total Brain Volume] under the NT, EC condition. The relationship between these two variables is significant with a Spearman rank correlation coefficient of 0.44 and p=0.012. With a positive correlation, as CC increases, ML VEL also increases.

3.1.5 Standing Balance, CHOL, and NON-CHOL

Finally, the Spearman rank correlation coefficient was used to determine the non-linear relationship between the outcome balance measures and CHOL and NON-CHOL across all three tasks and both eye conditions. There were no significant relationships between these variables. The Spearman coefficients and corresponding p-values are presented in the appendix, Table 17. The same relationships were reanalyzed to better understand if the difference in balance outcome measures was due to overall health by adjusting for gait speed within the statistical model. Again, there were no significant relationships between these variables. The adjusted Spearman correlation coefficients and their corresponding p-values are presented in the appendix, Table 17.

3.2 GAIT

3.2.1 Characteristics of Independent Predictor Variables

As with the standing balance analysis, three different groups were defined to include SAA, CHOL and NON-CHOL, and WMH. Table 13 provides the summary statistics of each independent variable of interest to better understand the dataset used for analysis. All variables pertaining to WM are shown as percentages of total brain volume.

Table 13: Summary statistics for independent variables used in gait analysis.

Independent Variable [units]	Mean	SD	Range
SAA [pmole mL atropine equivalent^{-1}]	0.50	0.62	0-2.05
CHOL [% Total Brain Volume]	0.000734	0.000678	0-0.00214
NON-CHOL [% Total Brain Volume]	0.0108	0.0109	0.00145-0.0319
WMH ALL [% Total Brain Volume]	0.112	0.104	0.00555-0.452
AACC [% Total Brain Volume]	0.0673	0.0478	0.00502-0.215
CC [% Total Brain Volume]	0.0395	0.0343	0-0.135
SS [% Total Brain Volume]	0.00391	0.00812	0-0.0364

3.2.2 Effects of Dual-Task on Gait

The effect of walking while performing a dual-task was investigated for all subjects within each analysis group through the use of a mixed linear regression model. A significant task effect was seen in all but two variables of interest. The p-values for task effects and results of the post-hoc analysis are presented in Table 14 with statistical significance indicated by an asterisk.

Table 14: Statistical analysis of all dependent gait variables of interest to determine task condition effects during gait (α=0.05). p-values are provided. Post-hoc results indicate which tasks were significantly different. Significance denoted by asterisk (*).

Gait Variable	Analysis Group	Task	Task Post-hoc
CV	SAA	0.0044 *	NT/F, NT/B
DSV	SAA	0.041 *	NT/B
STV	SAA	0.0002 *	NT/B
SEV	SAA	0.011 *	NT/F, NT/B
Average GS	SAA	<0.0001 *	NT/F, NT/B, F/B
CV	CHOL/NON-CHOL	0.120	
DSV	CHOL/NON-CHOL	0.60	
STV	CHOL/NON-CHOL	0.0013 *	NT/B, F/B
SEV	CHOL/NON-CHOL	0.011 *	NT/F, NT/B
Average GS	CHOL/NON-CHOL	<0.0001 *	NT/F, NT/B, F/B
CV	WMH	0.0063 *	NT/F, NT/B
DSV	WMH	0.048 *	NT/B
STV	WMH	0.0007 *	NT/F, NT/B
SEV	WMH	0.015 *	NT/F, NT/B
Average GS	WMH	<0.0001 *	NT/F, NT/B, F/B

These effects are further demonstrated graphically in Figures 14-18. For average GS, there is a significant decrease in GS between walking without a task and walking with a task. Additionally, there is a significant decrease in GS when walking between B and F. This was consistent across all analyses. For the SAA analysis, stance time and double support variability increased significantly between the NT and B conditions. Step time and cadence variability also increased significantly between the NT and B conditions but also increased significantly between the NT and F conditions. Across all variables, there was no significant difference between the F and B conditions. For the CHOL and NON-CHOL analysis, double support and cadence variability did not show any differences between tasks. Stance time variability showed a

significant increase in variability between NT and B and also between F and B. Step time variability showed increased variability between NT and F and NT and B. Finally, for the WMH analysis, stance time, step time, and cadence variability all showed a significant increase in variability between NT and F and NT and B. Double support time variability only showed a significant increase in variability between NT and B. Across all variables, there was no significant difference between the F and B conditions.

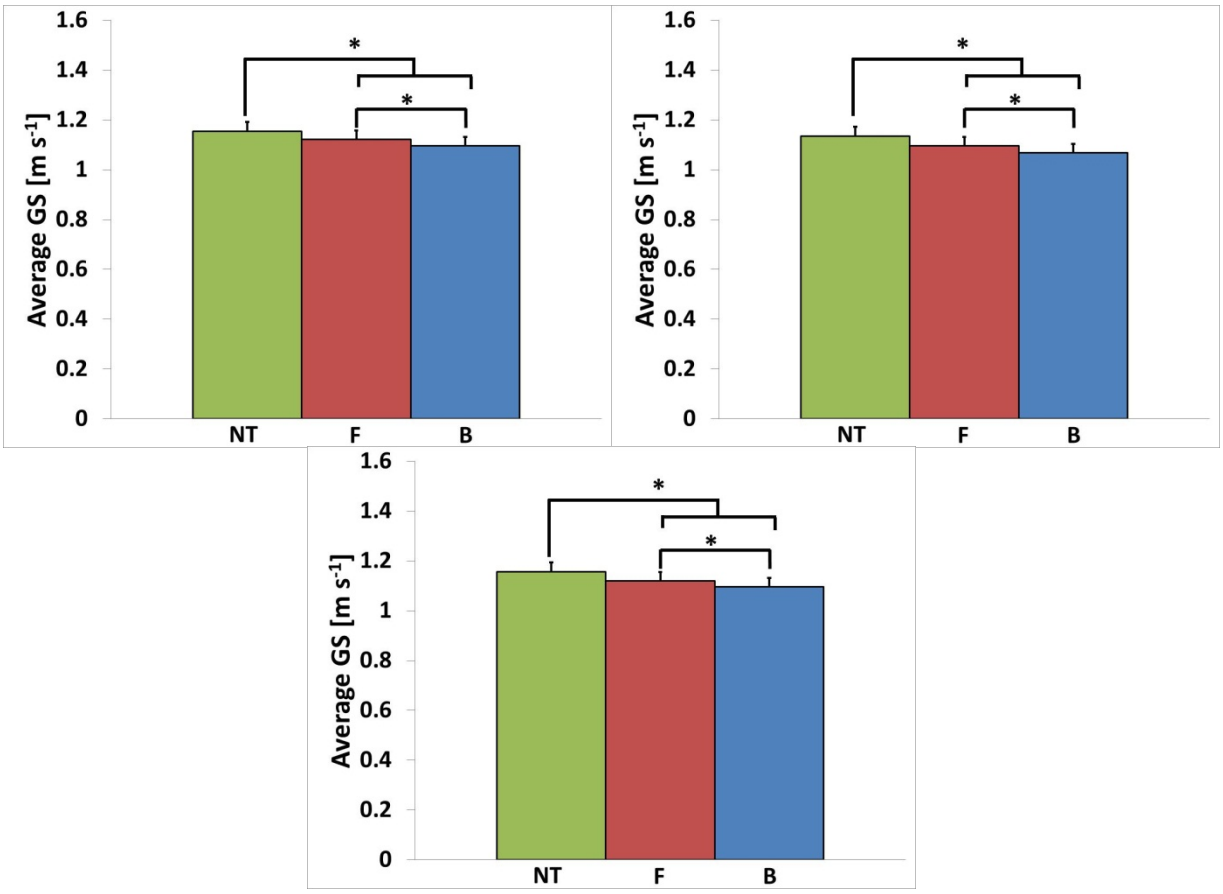

Figure 14: Average gait speed [m s^{-1}] across tasks for SAA analysis (top left), CHOL and NON-CHOL (top right), and WMH (bottom middle). Asterisk (*) indicates statistical significance between tasks. Standard error bars are shown.

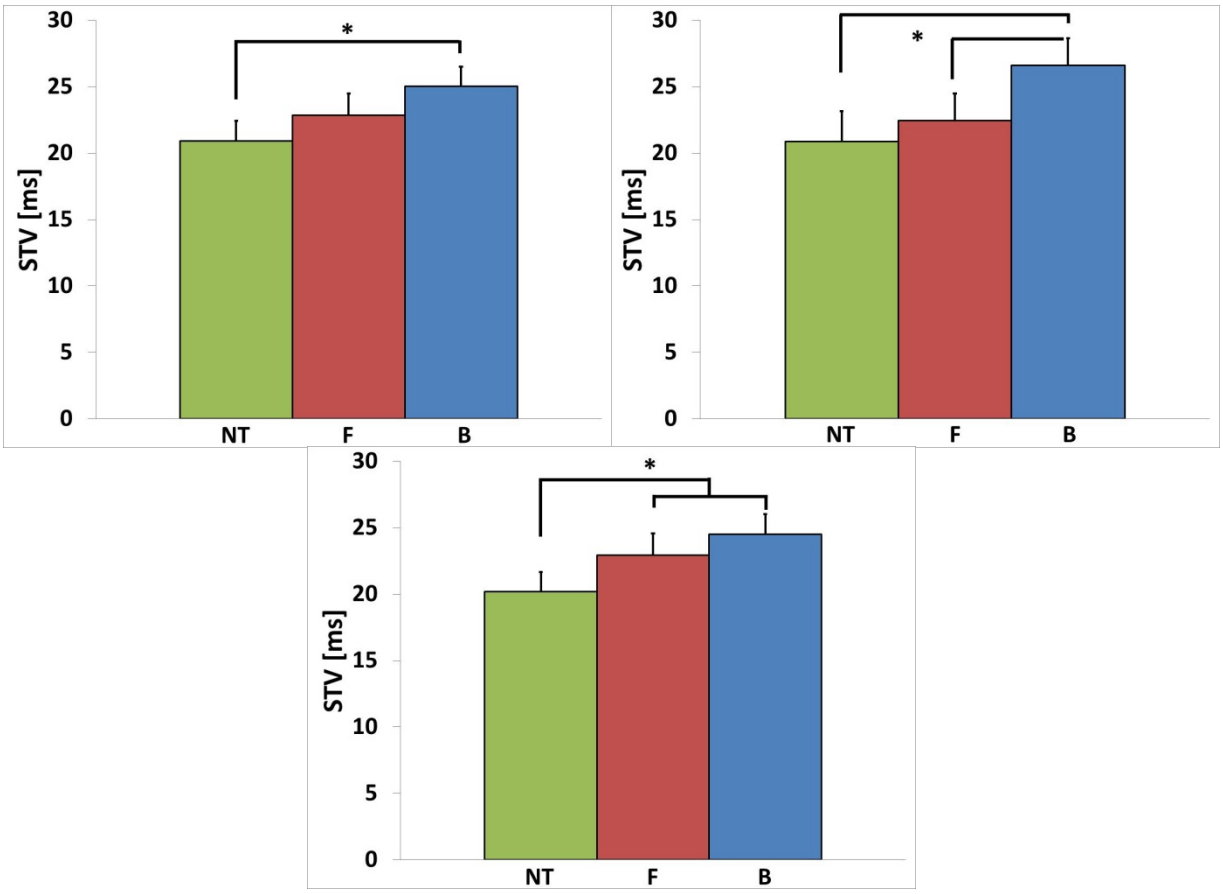

Figure 15: Average stance time variability [ms] across tasks for SAA analysis (top left), CHOL and NON-CHOL (top right), and WMH (bottom middle). Asterisk (*) indicates statistical significance between tasks. Standard error bars are shown.

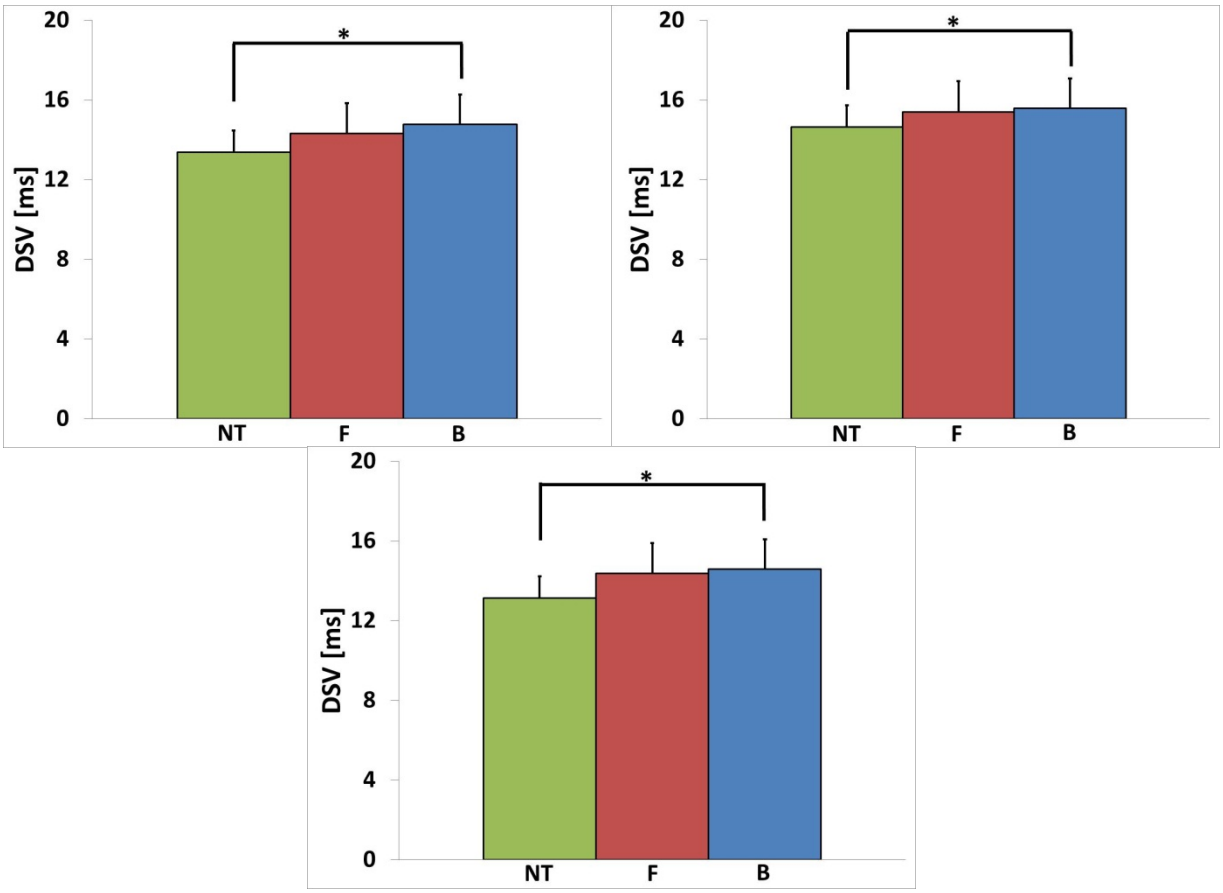

Figure 16: Average double support time variability [ms] across tasks for SAA analysis (top left), CHOL and NON-CHOL (top right), and WMH (bottom middle). Asterisk (*) indicates statistical significance between tasks. Standard error bars are shown.

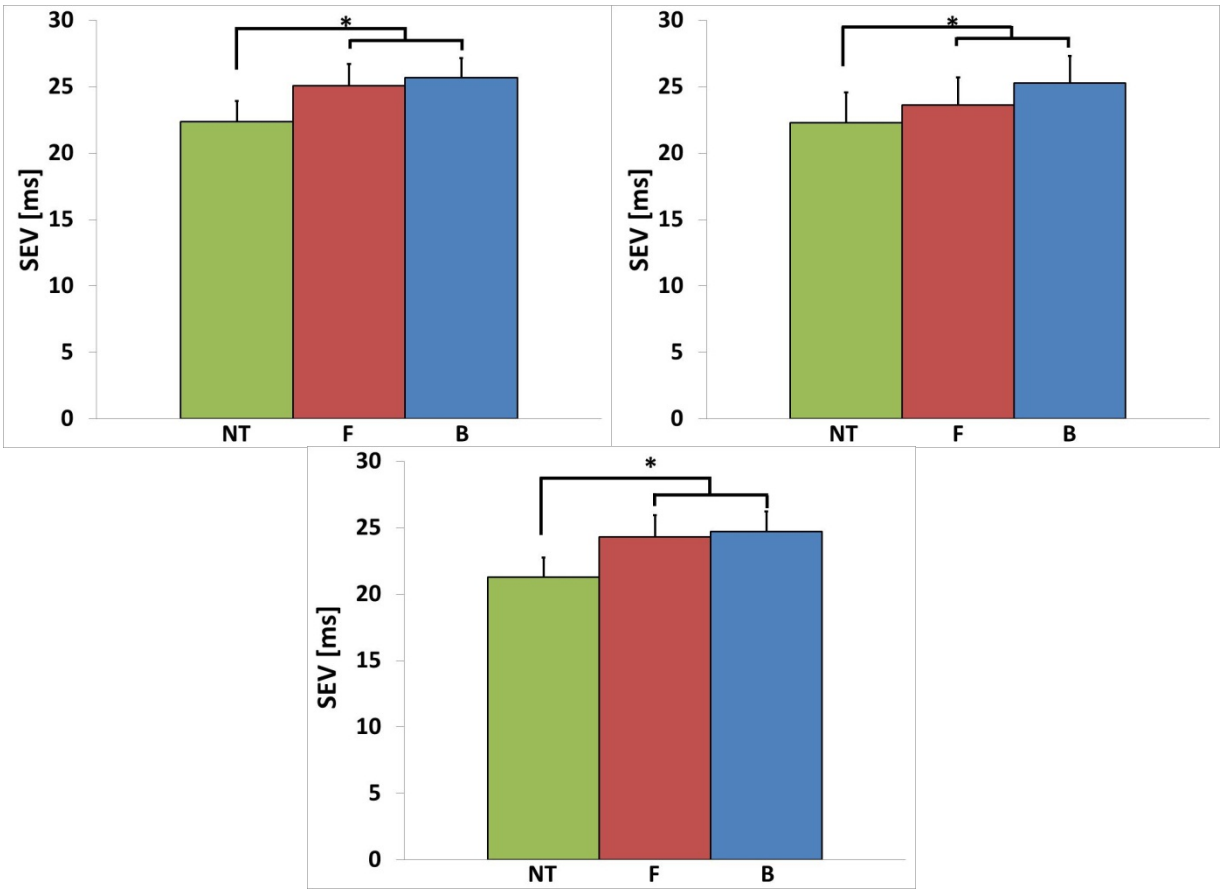

Figure 17: Average step time variability [ms] across tasks for SAA analysis (top left), CHOL and NON-CHOL (top right), and WMH (bottom middle). Asterisk (*) indicates statistical significance between tasks. Standard error bars are shown.

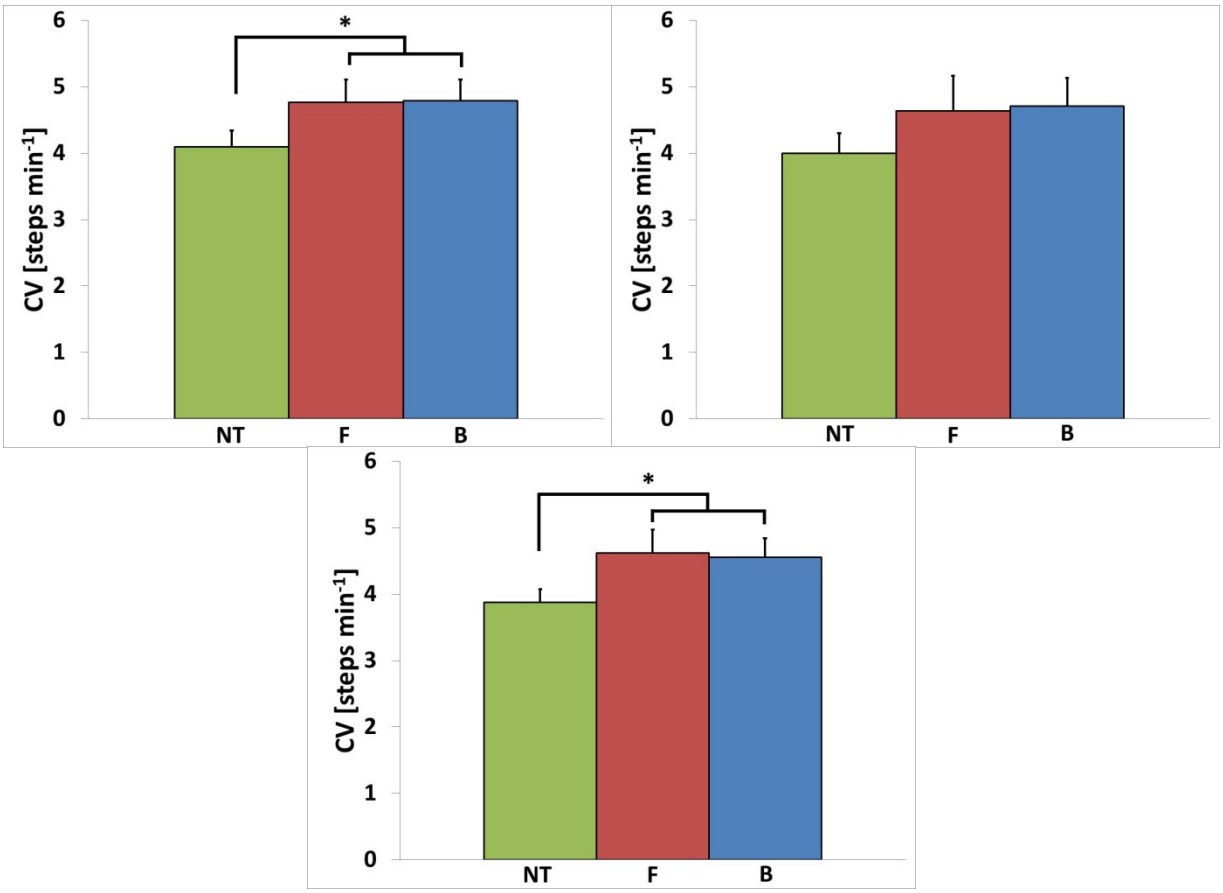

Figure 18: Average cadence variability [steps min^{-1}] across tasks for SAA analysis (top left), CHOL and NON-CHOL (top right), and WMH (bottom middle). Asterisk (*) indicates statistical significance between tasks. Standard error bars are shown.

3.2.3 Relationship between Gait Variability and the Predictor Variables

The relationship between the measures of gait variability and the predictor variables of interest was determined using the linear Pearson correlation coefficient. First, this analysis was done on average GS and the temporal variability parameters calculated across all task types. Average GS was not correlated with any of the predictor variables of interest across all tasks. However, it was determined that there was a positive, significant relationship between cadence variability and NON-CHOL without a dual-task, stance time variability and NON-CHOL without a dual-task, and step time variability and NON-CHOL without a dual-task or under the B condition. The relationship between the measures of gait variability and the predictor variables was again conducted but by adjusting for gait speed within the linear model. By adjusting for gait speed, it could be inferred if the differences in gait variability were due to health status. The average GS corresponding to the task of interest was used for each analysis. After adjusting for gait speed, there was again a positive significant relationship between cadence variability and NON-CHOL without a dual-task, stance time variability and NON-CHOL without a dual-task, and step time variability and NON-CHOL under the B condition. Additionally, stance time variability was also significantly related to SS under the F condition and step time variability was no longer related to NON-CHOL without a dual-task condition. As in standing balance, a positive correlation indicated an increase in gait variability with an increase in the predictor variables. The Pearson correlation coefficients and their associated p-values for both the unadjusted and adjusted analyses are presented in Table 15 for the significant conditions. All adjusted and unadjusted Pearson correlation coefficients are presented in the appendix, Table 18.

Table 15: Unadjusted and adjusted Pearson correlation coefficients and their corresponding p-values describing the relationship between the gait variability variables of interest and NON-CHOL and SS (α=0.05) for all tasks. Significance is denoted by an asterisk (*).

Task	Variability Measure	Predictor Variable	Unadjusted Pearson Coefficient	Unadjusted Pearson p-value	Adjusted Pearson Coefficient	Adjusted Pearson p-value
NT	CV	NON-CHOL	0.56	0.01 *	0.56	0.012 *
NT	CV	SS	0.095	0.61	0.096	0.61
F	CV	NON-CHOL	-0.024	0.91	-0.027	0.91
F	CV	SS	0.037	0.84	0.039	0.83
B	CV	NON-CHOL	0.16	0.49	0.19	0.45
B	CV	SS	0.042	0.82	0.046	0.81
NT	STV	NON-CHOL	0.58	0.0075 *	0.57	0.010 *
NT	STV	SS	0.053	0.77	0.077	0.68
F	STV	NON-CHOL	0.046	0.85	-0.046	0.85
F	STV	SS	0.32	0.070	0.37	0.038 *
B	STV	NON-CHOL	0.35	0.13	0.26	0.29
B	STV	SS	0.023	0.89	0.051	0.79
NT	SEV	NON-CHOL	0.49	0.027 *	0.45	0.051
NT	SEV	SS	0.12	0.49	0.15	0.43
F	SEV	NON-CHOL	0.10	0.67	0.010	0.97
F	SEV	SS	0.21	0.25	0.250	0.18
B	SEV	NON-CHOL	0.59	0.0088 *	0.54	0.021 *
B	SEV	SS	0.18	0.34	0.23	0.21

Figures 19-22 further graphically demonstrate the significant relationships between three of the gait variability measures and the NON-CHOL during NT and B.

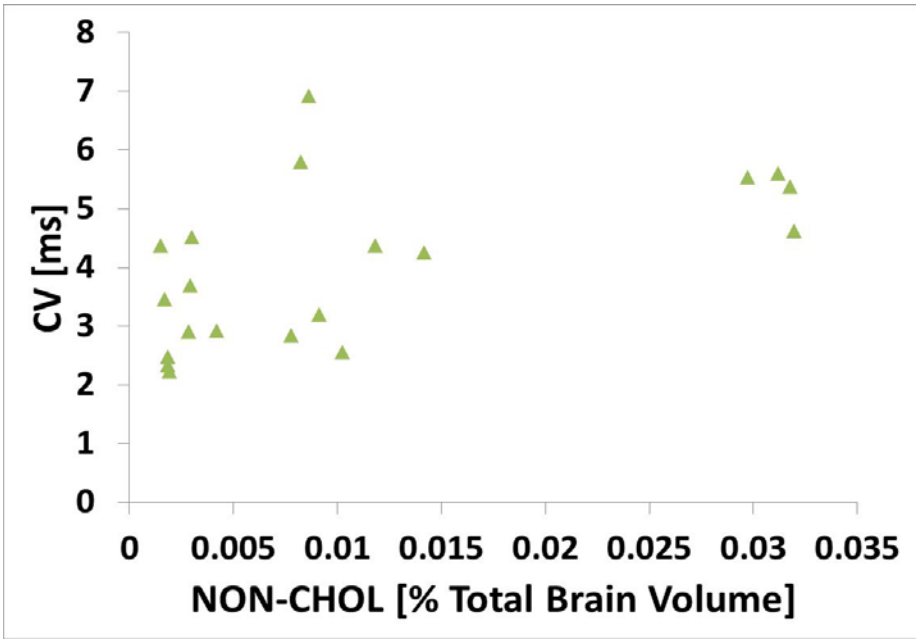

Figure 19: CV [steps min^{-1}] vs. NON-CHOL [% Total Brain Volume] during NT. The relationship between these two variables is significant with a Pearson correlation coefficient of 0.56 and p=0.01. With a positive correlation, as NON-CHOL increases, CV also increases.

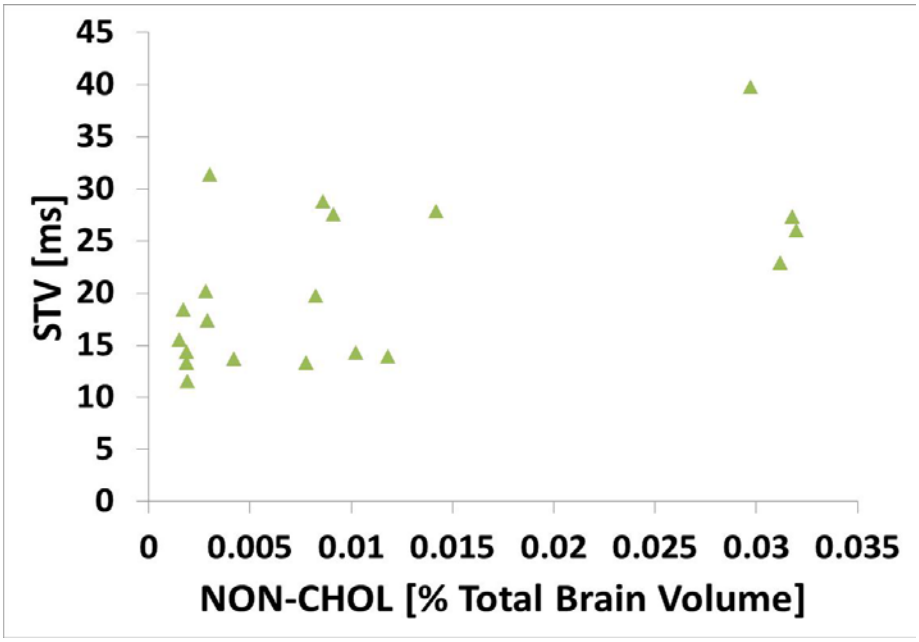

Figure 20: STV [ms] vs. NON-CHOL [% Total Brain Volume] during NT. The relationship between these two variables is significant with a Pearson correlation coefficient of 0.57 and p=0.0075. With a positive correlation, as NON-CHOL increases, STV also increases.

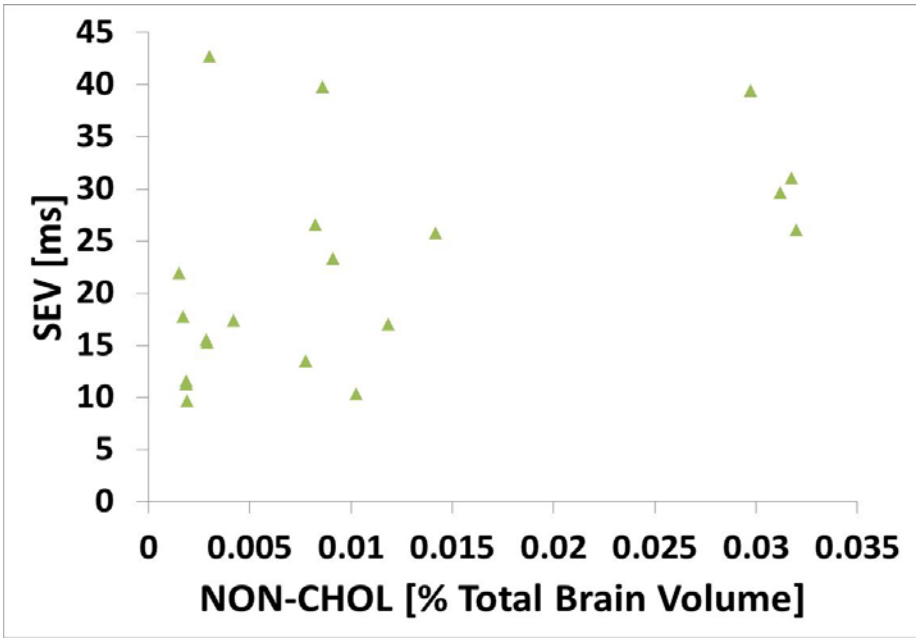

Figure 21: SEV [ms] vs. NON-CHOL [% Total Brain Volume] during NT. The relationship between these two variables is significant with a Pearson correlation coefficient of 0.49 and p=0.027. With a positive correlation, as NON-CHOL increases, SEV also increases.

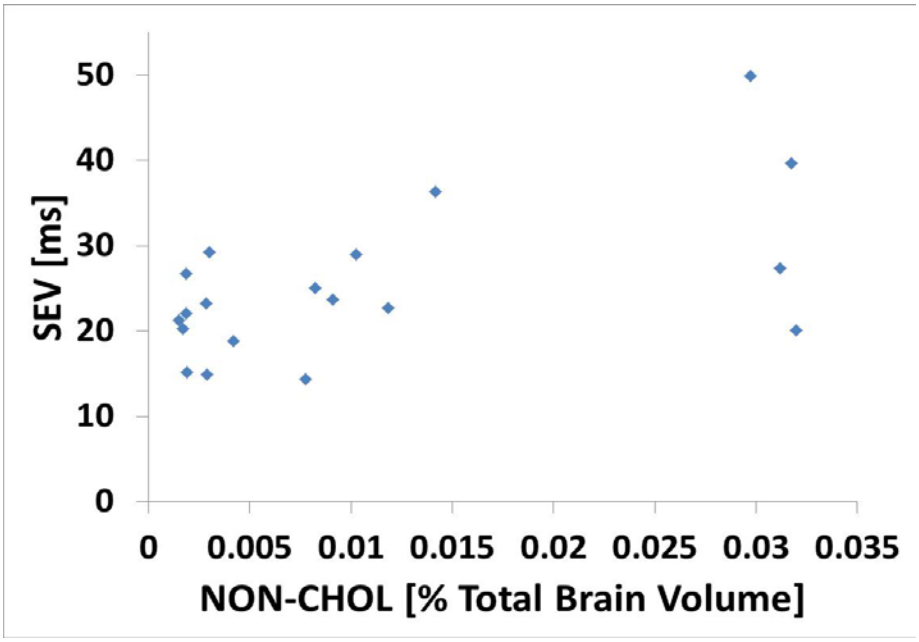

Figure 22: SEV [ms] vs. NON-CHOL [% Total Brain Volume] during B. The relationship between these two variables is significant with a Pearson correlation coefficient of 0.59 and p=0.0088. With a positive correlation, as NON-CHOL increases, SEV also increases.

3.2.4 Explanation of Gait Variability by Predictor Variables and Gait Speed

As mentioned previously, regression analyses were used to determine the contributions of both the predictor variables and gait speed to the explanation of gait variability. By using the R^2 difference between the first model with average GS only and the third model with the predictor variable of interest and average GS, the added value of the predictor variable could be quantified. With regards to cadence, regression analyses revealed that when experiencing the NT condition, NON-CHOL explained over 32% of the variability above and beyond that explained by average GS. With regards to double support, regression analyses demonstrated that under the NT condition, NON-CHOL, SAA, WMH ALL, and CC all significantly contributed to the

explanation of the variability in double support time above and beyond that explained by average GS with NON-CHOL explaining the most at 9%. All predictor variables showed a significant contribution to stance time variability under NT with NON-CHOL most notably accounting for 21% of the variability above that explained by gait speed. All but CHOL and NON-CHOL were also significant for stance time variability under the F condition and all but CHOL were significant for stance time variability under the B condition. Finally, when looking at step time variability, all predictor variables except for CHOL showed a significant contribution when not experiencing a dual-task or under the B condition. When not given a task, NON-CHOL explained 16% of the step time variability above beyond that explained by gait speed while when given a B task, NON-CHOL explained 24%. Under the F condition, all predictor variables other than CHOL and NON-CHOL showed significant contributions. Interestingly, across all tasks and gait variability measures, NON-CHOL seemed to account for the most variability in gait variability measures above and beyond that explained by gait speed. The significant variables of interest are presented in Table 16 while all values for the complete regression analysis are presented in the appendix, Table 19.

Table 16: R^2 values obtained by regressing each gait variability measure on average GS alone (A), each predictor variable alone (B), and on average GS and each predictor variable combined (C). The added value of each predictor variable is quantified using the R^2 difference between models C and A. Statistical significance of the combined effects was set at α=0.05 and is denoted by an asterisk (*).

Task	Variability Measure	Predictor Variable	GS Only (A)	Predictor Only (B)	GS & Predictor (C)	ΔR^2 (C-A)	p-value of ΔR^2
NT	CV	NON-CHOL	0.0037	0.32	0.32	0.32	0.038 *
NT	DSV	NON-CHOL	0.22	0.16	0.31	0.09	0.042 *
NT	DSV	SAA	0.22	0.0036	0.25	0.03	0.0054 *
NT	DSV	WMH ALL	0.15	0.028	0.20	0.05	0.0337 *
NT	DSV	CC	0.15	0.033	0.21	0.06	0.026 *
NT	STV	CHOL	0.35	0.0055	0.35	0	0.024 *
NT	STV	NON-CHOL	0.35	0.33	0.56	0.21	0.0009 *
NT	STV	SAA	0.41	0.0091	0.42	0.01	<0.0001 *
NT	STV	WMH ALL	0.38	0.019	0.42	0.04	0.0002 *
NT	STV	AACC	0.38	0.001	0.40	0.02	0.0004 *
NT	STV	CC	0.38	0.0088	0.41	0.03	0.0003 *
NT	STV	SS	0.35	0.0028	0.36	0.01	0.0016 *
F	STV	SAA	0.26	0.077	0.30	0.04	0.0015 *
F	STV	WMH ALL	0.20	0.0021	0.21	0.01	0.028 *
F	STV	AACC	0.20	0.0001	0.21	0.01	0.028 *
F	STV	CC	0.20	0.0027	0.21	0.01	0.025 *
F	STV	SS	0.21	0.11	0.32	0.11	0.0037 *
B	STV	NON-CHOL	0.26	0.12	0.31	0.05	0.045 *
B	STV	SAA	0.32	0.0002	0.33	0.01	0.0007 *
B	STV	WMH ALL	0.32	0.016	0.36	0.04	0.001 *
B	STV	AACC	0.32	0	0.34	0.02	0.0018 *
B	STV	CC	0.32	0.033	0.38	0.06	0.0005 *
B	STV	SS	0.33	0.0005	0.33	0	0.0027 *
NT	SEV	NON-CHOL	0.21	0.24	0.37	0.16	0.019 *
NT	SEV	SAA	0.25	0.006	0.25	0	0.0053 *
NT	SEV	WMH ALL	0.23	0.0075	0.24	0.01	0.013 *

Table 16 (continued)

NT	SEV	AACC	0.23	0.001	0.23	0	0.018 *
NT	SEV	CC	0.23	0.0052	0.25	0.02	0.013 *
NT	SEV	SS	0.21	0.015	0.23	0.02	0.023 *
F	SEV	SAA	0.20	0.030	0.21	0.01	0.014 *
F	SEV	WMH ALL	0.18	0.0022	0.18	0	0.047 *
F	SEV	AACC	0.18	0.0027	0.19	0	0.046 *
F	SEV	CC	0.18	0.0041	0.18	0	0.047 *
F	SEV	SS	0.21	0.046	0.26	0.05	0.015 *
B	SEV	NON-CHOL	0.19	0.34	0.43	0.24	0.012 *
B	SEV	SAA	0.21	0.012	0.24	0.03	0.0077 *
B	SEV	WMH ALL	0.25	0.0097	0.28	0.03	0.0075 *
B	SEV	AACC	0.25	0	0.27	0.02	0.0099 *
B	SEV	CC	0.25	0.0049	0.27	0.02	0.0088 *
B	SEV	SS	0.29	0.032	0.33	0.04	0.0036 *

To further explain these results, two plots were generated for a select sub-set of the significant relationships between gait speed and the predictor variable on gait variability, and they can be found in figures 23-27. For all figures, the plot on the left represents the predictor variable plotted against average GS, demonstrating average GS's contribution to the variability. The plot on the right represents the residuals of the dependent gait variability measure plotted against the predictor variable of interest, demonstrating the contribution of the predictor variable to explaining the variability in the gait measure above and beyond that explained by average GS.

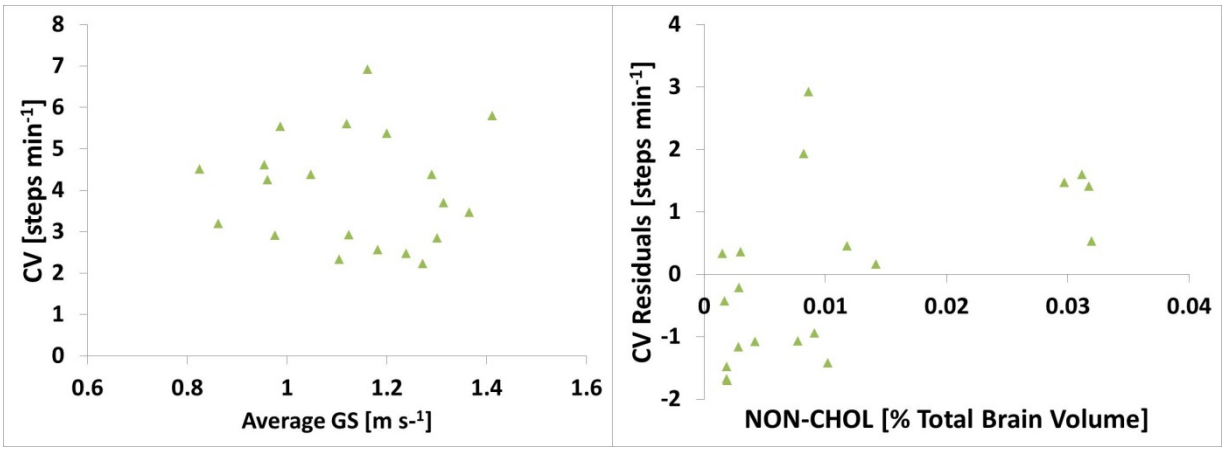

Figure 23: On left, CV [steps min^{-1}] vs. Average GS [m s^{-1}] under NT condition. ΔR^2=0.0037. On right, the average GS adjusted residuals of CV [steps min^{-1}] are plotted against NON-CHOL [% Total Brain Volume] under NT condition. ΔR^2=0.32. Thus, 32% of the variability in cadence variability is explained by NON-CHOL under NT above and beyond that explained by average GS.

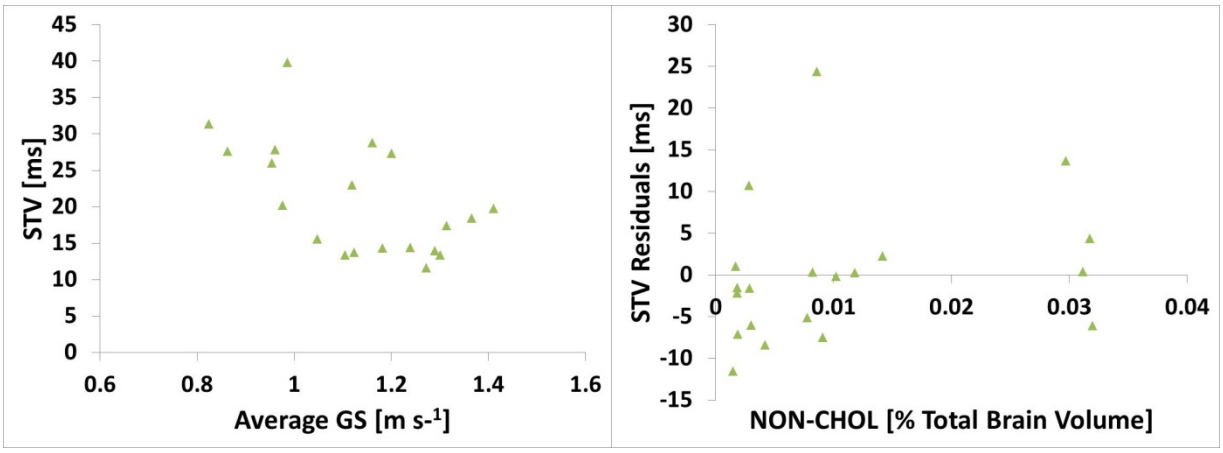

Figure 24: On left, STV [ms] vs. Average GS [m s^{-1}] under NT condition with R^2=0.35. On right, the average GS adjusted residuals of STV [ms] are plotted against NON-CHOL [% Total Brain Volume] under NT condition. ΔR^2=0.21. Thus, 21% of the variability in stance time variability is explained by NON-CHOL under NT above and beyond that explained by average GS.

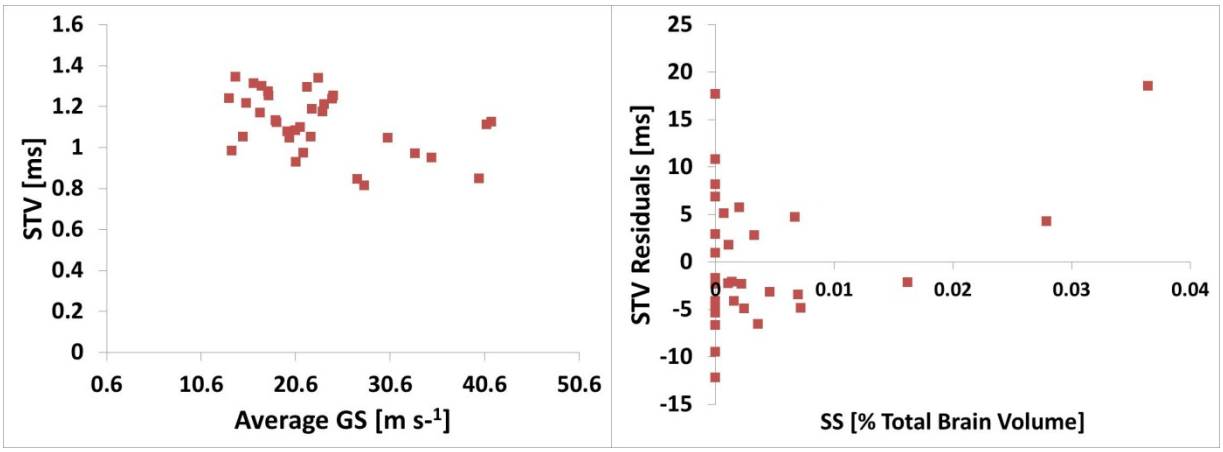

Figure 25: On left, STV [ms] vs. Average GS [m s^{-1}] under F condition with R^2=0.21. On right, the average GS adjusted residuals of STV [ms] are plotted against SS [% Total Brain Volume] under F condition. ΔR^2=0.11. Thus, 11% of the variability in stance time variability is explained by SS under F above and beyond that explained by average GS.

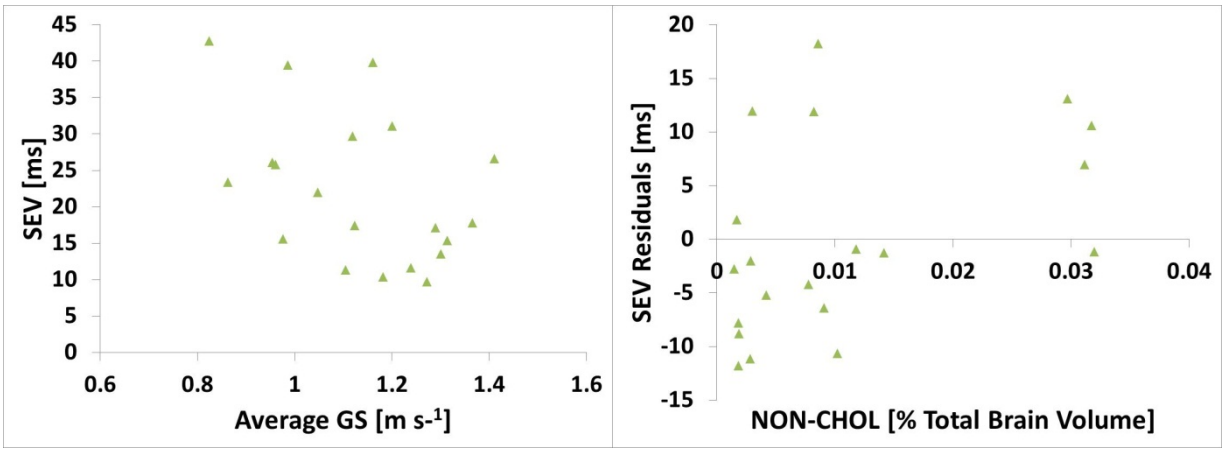

Figure 26: On left, SEV [ms] vs. Average GS [m s^{-1}] under NT condition with R^2=0.21. On right, the average GS adjusted residuals of SEV [ms] are plotted against NON-CHOL [% Total Brain Volume] under NT condition. ΔR^2=0.16. Thus, 16% of the variability in step time variability is explained by NON-CHOL under NT above and beyond that explained by average GS.

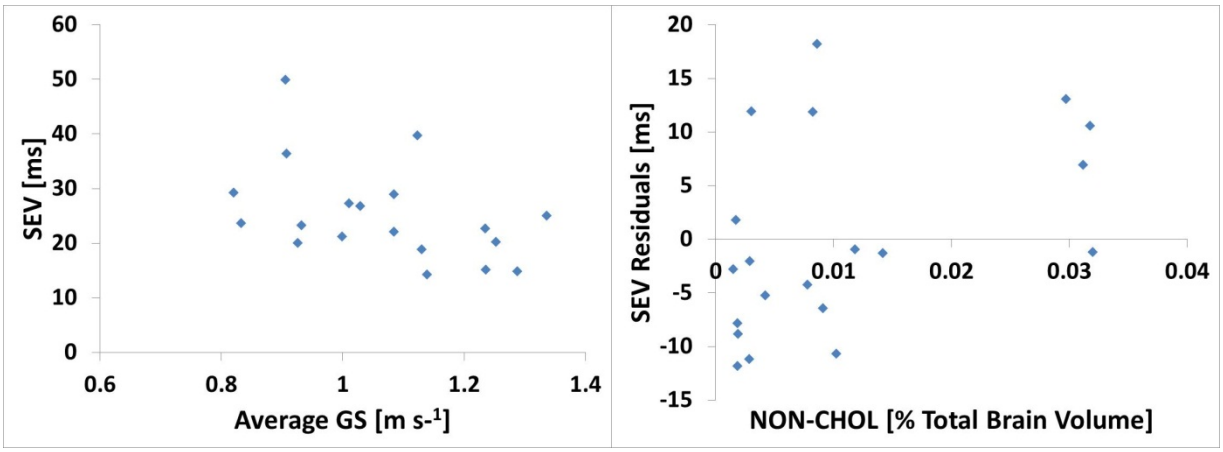

Figure 27: On left, SEV [ms] vs. Average GS [m s^{-1}] under B condition with R^2=0.19. On right, the average GS adjusted residuals of SEV [ms] are plotted against NON-CHOL [% Total Brain Volume] under B condition. ΔR^2=0.24. Thus, 24% of the variability in step time variability is explained by NON-CHOL under B above and beyond that explained by average GS.

4.0 DISCUSSION

4.1 STANDING BALANCE

4.1.1 Overall Balance Performance

The first analysis conducted on the balance outcome measures involved understanding the effects of two different eye conditions and three different task conditions on standing balance. As consistent with previous research, there was an increase in sway in the ML and AP directions, increased speed in both directions, and increased overall distance travelled when standing with eyes closed compared to eyes open (Nagano et al., 2006; Prado et al., 2007; Hansson et al., 2010; Strang et al., 2011). However, task effects were only seen in five out of the fifteen variables analyzed. In general, participants swayed more and in the AP direction when not performing a dual-task compared to performing a F task. They also swayed faster in the AP direction when not performing a task compared to a B task. It was originally hypothesized that balance performance would decrease (i.e. increased sway, velocity, and distance) when performing a cognitive challenge task due to the added attention demands required to perform both tasks. These results do not support this hypothesis. Previous research demonstrates conflicting results. When performing a visual dual-task, the amount and velocity of sway decreased in older adults according to Prado and colleagues (2007). According to Shumway-Cook and Woollacott (2000),

during a cognitively challenging auditory task, there were no significant changes in balance outcome measures in healthy older adults compared to standing balance without a task. However, Maylor and Wing (1996) and Teasdale and Simoneau (2001) found sway to increase in healthy older adults when performing a cognitive challenge task during quiet stance. The results of this research project and the discrepancy in previous work may reference back to the statement by Bloem and colleagues (2001) that older adults prioritize maintaining balance over successful completion of the secondary task, possibly to avoid falling. If this were true, the participants used in this analysis would have decreased accuracy in recalling the digits to better maintain balance while participants in the studies that saw increased sway and decline in balance would have maintained accuracy performance with the cognitive task while sacrificing balance.

Further work must be conducted to identify if participants used for this study did in fact sacrifice accuracy of performance to better maintain balance. If accuracy is not found to be one potential cause, it may also be hypothesized that balance was quantitatively worse when not performing a task due to the long duration of the trial and the participant simply asked to stand as still as possible. Participants may have fatigued throughout the duration of each 60 second trial. Even though they were provided seated rest breaks as often as requested, some participants reported boredom over time with “just having to stand there”, which may have hindered their performance. Participants may also have not been focusing on balance when not performing a task but rather simply maintaining an upright posture, which could still result in significant sway outcomes. Furthermore, the limited statistical significance between tasks and the absence of any interaction effects of task and vision condition may further be explained by overall participant health. The screening process utilized to determine eligibility maintained strict requirements so as to not recruit participants of poor mental or physical health status. By including fit, active

older adults and excluding those with known conditions, the results may better reflect conclusions seen in younger adults.

4.1.2 Standing Balance and SAA

Part of the goal of Specific Aim 1 was to identify the relationship between SAA and balance outcome measures during single-task quiet stance and while performing a concurrent cognitive task under two different eye conditions. While the exact mechanism of action of SAA on causing a decline in balance is unknown, as previously mentioned, SAA has been linked to a decrease in cognitive function, attention, and processing speed. Pilot work has also demonstrated increased sway with increased SAA levels. Based on this prior knowledge, it was hypothesized that balance performance would decrease with increased levels of SAA and that this relationship would be enhanced when analyzed under a dual-task condition. This relationship was determined using the Spearman correlation coefficient. According to our results, no significant relationships were found between balance outcome measures and SAA, regardless of task or eye condition. Interestingly, out of the 30 correlations between SAA and the five balance outcome measures for all conditions, 26 of these correlations were negative, indicating a trend towards improved balance with increased SAA. In fact, the strongest negative correlation was -0.25 (ML RMS with EO and B) while the strongest positive correlation was only 0.097 (AP RMS with EC and NT). Even when accounting for overall health status by adjusting for gait speed, no significant relationships were found between SAA and balance outcome measures. Again, out of the 30 correlations between SAA and the five balance outcome measures for all conditions, 26 of these were negative. Correlations in both directions had negligible changes with the strongest negative correlation decreasing to -0.24 and the strongest positive correlation increasing to 0.11. Since

there was no change in the results when adjusting for gait speed, it can be concluded that overall health condition does not affect the relationship between SAA and the outcome measures of standing balance regardless of task or eye condition. These results are inconsistent with the initial hypothesis and the previous pilot work.

The absence of significant findings within the participants recruited for this analysis may be due to their overall health, cognitive status and lack of anticholinergic medication use. The participants included in this analysis had SAA levels averaging 0.54 pmole mL atropine equivalent^{-1} and ranging from 0-2.05 pmole mL atropine equivalent^{-1}. This is much lower compared to previous literature using the same technique for quantifying SAA level. Participants recruited for work done by Mulsant and colleagues with age range of 71-95 years had average SAA levels of 1.50 pmole mL atropine equivalent^{-1} and ranged from 0.5-5.70 pmole mL atropine equivalent^{-1} (Mulsant et al., 2003). Participants used in work by Nebes and colleagues had an average age of 72.1 years and average SAA level of 1.72 pmole mL atropine equivalent^{-1} (Nebes et al., 2011). The pilot work completed prior to this study and showing a significant relationship to balance carried a very high average SAA level of 1.76 pmole mL atropine equivalent^{-1} and range of 1.2-2.6 pmole mL atropine equivalent^{-1}. Even though the high end of our range is almost equal to that of the pilot work, only 11 of the 44 participants had SAA levels larger than 1 pmole mL atropine equivalent^{-1} while 21 participants had undetectable SAA levels.

Without a large variance of SAA levels and very few participants at moderate to higher levels, the participants in this work may not have experienced any negative effects or only experienced slight effects associated with the use of anticholinergic medications such as a decline in cognitive function or attention. Since dual-tasking while standing requires additional cognitive demands and attention (Pellecchia, 2005), it would have been expected that with

increased cognitive load from performing both tasks, participants at higher SAA levels would have seen a decline in balance due to the negative cognitive impact associated with SAA. Because this was not seen and the SAA levels are so low with a small variance in the participants used in this research, we can conclude that SAA level is not able to explain the significant changes seen in the participants' balance between eye and task conditions. Again, this may be due to the fact that the participants recruited for this work were screened for overall health and free from cognitive deficits.

4.1.3 Standing Balance and WMH

Part of the goal of Specific Aim 2 was to investigate the relationship between WMH and balance during single-task quiet stance and stance performed under a dual-task for both eyes open and eyes closed. As with SAA, the mechanism of action is not clearly understood. Previous research by Sparto and colleagues (2008) is the only known work to associate WMH to quantitative balance measures through step initiation tasks, finding increased WMH levels to be associated with impaired balance. It was hypothesized that balance would decline with increased levels of overall WMH and increased levels of WMH in the individual tracts of interest, and that this relationship would be amplified when performing a task with eyes close. As with SAA, the relationship between balance and the WMH predictor variables was found using the Spearman correlation coefficient. Our results indicate that ML RMS significantly increased when standing with EC under NT when WMH ALL, AACC, and CC also increased. ML VEL also increased with increased CC during the NT, EC condition. No significant relationships were seen with EO or during a dual-task. The lack of EO correlations could be due to the overall decrease in balance performance in the participants when standing with EC compared to EO as previously described.

It was interesting that significant relationships were not seen with PL during these same correlations; however this could be due to the fact that RMS was only significant in one direction and PL is dependent on both the AP and ML directions. When adjusting for overall health using average gait speed, the only additional significant relationship was seen during EC with NT in AP RMS. It is very important to note that out of 120 correlations between balance outcome measures and WMH across all tasks and eye conditions, only five of these correlations (4.2%) were significant when unadjusted for gait speed and six out of 120 correlations (5%) were significant when adjusted for gait speed. With this, the significance in these results may actually be due only to chance rather than actual relationships with WMH.

The absence of more significant findings from this analysis may again be attributed to overall participant health as was true with the SAA analysis. According to Debette and Marcus (2010), 11-21% of healthy adults have detectable WMH found on MRI at the age of 64. The average percent of total brain volume that contained WMH was 0.104% and ranged from 0.00219-0.542%. The largest contribution to the total WMH from the combination of tracts used was from AACC which had an average of 0.0582% and range from 0-0.215%. The smallest contribution to the total WMH was from SS which had an average of only 0.00342% and range from 0-0.0595%. In fact, 14 of the 40 participants had undetectable WMH in the SS region. Unfortunately, these values are extremely difficult to compare to previous literature given the custom algorithm used to semi-automatically quantify WMH as a percentage of total brain volume. Most authors grade MRI based on a qualitative scale or determine WMH as a volumetric measurement rather than a percentage of total brain volume using a voxel count. Two references were found in which WMH was quantified as a percentage of total brain volume. First, the work of Sparto and colleagues (2008) was the only source that used the same method of

analyzing the participant MRI scans. The only region of interest used was AACC which had a range of 0.1-3.1% total brain volume in the tracts making up this region. This is much higher than the range found in this study with our high end range being 14 times less than their high end range. Second, Burton and colleagues (2006) found an overall WMH average in healthy older adults to be 0.4% total brain volume with a range of 0.2-1.2% total brain volume. Both the average value and high end range were twice that of our participant population generating higher WMH levels and a larger variance.

Without a larger variance of WMH values and such low percentages of total brain volume, it can be inferred that balance in these participants is not impacted by WMH. With such a high health status for older adults and low levels of WMH, the participants in this project may have very limited or even no effects previously associated with WMH. For example, demyelination, loss of axons, gliosis, and dilation of the periventricular space have all been associated with WMH (Ota et al., 2010). Physiological consequences associated with these changes may then include neuronal slowing and delay of signal processing. Ultimately, this may lead to motor slowing (Murray et al., 2010). If higher levels of WMH were to be seen in this population and positive correlations existed, chances are quite likely that these participants would have experienced some form of motor slowing, thus preventing them from maintaining consistent upright stance. Balance maintenance is a dynamic process requiring continuous feedback and execution in response to changes in position within space. Damage to the areas such as the cortex, thalamus and basal ganglia as a result of WMH have been shown to interfere with motor output to the lower extremities during balance tasks (Hennerici et al. 1994; Tell et al. 1998; Guttmann et al. 2000; Wolfson 2001). Since the regions of interest selected for this analysis are associated with those areas along with being linked to some aspect of motor control

including modulation, attention, and executive function (Sheline et al., 2008; Sparto et al., 2008; Duering et al., 2011), we should see the expected decline in balance if the average and variance of WMH as a percent of total brain volume was much larger for the participant population recruited, especially when standing with a dual-task.

4.1.4 Standing Balance and the Combined Effects of SAA and WMH

The first portion of Specific Aim 3 looked to determine if there was a relationship between standing balance under different task and eye conditions with the combined effects of SAA and WMH. This was accomplished using the volume of WMH located in the CHOL and NON-CHOL tracts as determined by MRI. Again, CHOL are the tracts containing cholinergic fibers while NON-CHOL are the tracts not containing cholinergic fibers. It was hypothesized that participants taking anticholinergic medications who also showed the presence of WMH within the cholinergic tracts would have decreased balance performance, and this decrease would be exaggerated when standing while performing a task with eyes closed. Using the Spearman correlation, our results indicate that there were no significant relationships between the balance outcome measures and CHOL or NON-CHOL across all tasks and both eye conditions. These results held constant when adjusting for gait speed to control for overall health status.

Previous research has indicated through the use of human and animal models that with the presence of WMH in cholinergic pathways, the susceptibility to anticholinergic effects becomes amplified (Flicker et al., 1992; Ray et al., 1992). This means that if a participant was to have WMH present within the white matter tracts containing cholinergic fibers, the effects of anticholinergic medications on balance and gait should be amplified. However, the results obtained here are not consistent with our hypothesis but are not surprising. To see results within

CHOL and NON-CHOL we would have expected to see more significant relationships between balance outcome measures and WMH since WMH is the main contribution to these tracts. Additionally, to obtain the correlations with CHOL, the results from correlations with SAA would also have to be significant. We were interested in identifying if the anticholinergic burden would be amplified due to WMH in this region, but without anticholinergic burden found in these participants, the CHOL tract properties would more reflect that of NON-CHOL since it is simply WMH, which did not show any significant results. It is again important to note that eight of the 21 participants used in this analysis had undetectable WMH in CHOL while the average was extremely small at 0.000656% of total brain volume. This value could almost be considered 0%. We can conclude from this that the participants used in this analysis did not experience balance impairments due to the combined effects of WMH and SAA. These conclusions can be further strengthened by the characteristics of the population used for this work in which overall health status was maintained and little magnitude and variance existed in both WMH and SAA.

4.2 GAIT

4.2.1 Overall Gait Performance

The first analysis executed on the spatiotemporal gait characteristics was done to understand the gait of the participants used in this research project and also to determine the effect of dual-tasking on gait. When comparing average GS and the average temporal variability parameters within each task condition to previous literature, our results fall well within range of those values previously published involving gait variability in healthy, older, non-fallers (Menz et al., 2003;

Brach et al., 2010; Calisaya et al., 2011; Hollman et al., 2011). Using a mixed linear regression, the dual-task effect of spatiotemporal gait characteristics was determined. Average GS was significantly different between single and dual-task conditions along with a difference between the F and B condition. STV and DSV were significantly different between NT and B. SEV and DSV were significantly different between NT and B and NT and F except for DSV in the CHOL/NON-CHOL analysis. All parameters of interest showed a trend or significant findings toward decreased gait speed and increased variability when walking with a dual-task compared to single-task. These results are consistent with previous work demonstrating decreased gait speed and increased variability when walking while performing a cognitive challenge task (Hausdorff et al., 2003; Sheridan et al., 2003; Beauchet et al., 2005; Hollman et al., 2007). In fact, according to Hollman and colleagues (2007), gait variability is impacted by dual-task conditions even without the presence of cognitive impairment, which is indeed a characteristic of our participant population.

The decrease in average GS while performing a task may be attributed to compensation during gait (Hollman et al., 2007). Through the use of this mechanism, participants may be able to maximize stability in walking by simply slowing down. By decreasing speed and creating a more stable environment, participants may be working to better cope with the cognitive challenges of the dual-task. However, a decrease in gait speed has been considered a contribution to falls (Luukinen et al., 1995; Cesari et al., 2005; Montero-Odasso et al., 2005). The increase in gait variability may be due to the interference of the task on gait due to competition of both the task and maintenance of consistent walking for available attention. Attention is independently required to perform a cognitive task and to walk under normal conditions. With a limited attention capacity, burdening the available resources by requiring more attention to perform

concurrent tasks could explain the changes seen here. Falls in older adults have been associated with activities requiring divided attention between two tasks such as walking while talking (The prevention of falls in later life, 1987; Bergland et al., 1998).

It must be noted that instructions given to participants did not favor performance on either the cognitive challenge task or gait. Participants were simply instructed to walk at a normal pace while performing the task. While it was not directly implied that accuracy was being measured, it is unknown if participants favored one task over the other. Further investigations must be conducted to understand if participants sacrificed their gait for accurate performance on the task or if their gait is truly this variable when performing a task regardless of accuracy. Because attention is limited and two sources were competing for what was available to these participants, degradation in one or both may be seen (Abernethy, 1988; Pashler, 1994; Beauchet & Berrut, 2006).

4.2.2 Spatiotemporal Gait Characteristics and SAA

The second part of Specific Aim 1 was to investigate the relationship between SAA and spatiotemporal gait parameters during single and dual-task conditions. As mentioned previously, the mechanism of action of SAA to impact characteristics of gait is not well understood. Previous research has shown a link between increases in SAA with decreased mobility. However, these analyses were conducted using objective assessments such as the SPPB and the Health ABC performance score. While both assessments provide insight into overall health and mobility, the sensitivity of objective assessments may not be as adequate as the quantitative assessments of gait measures used here to distinguish more subtle differences in normal walking among older adults. For example, the SPPB looks to analyze gait performance by scoring

participants on walking speed over a four meter walk. While decreased gait speed during normal walking has been shown to increase fall risk (Luukinen et al., 1995; Cesari et al., 2005; Montero-Odasso et al., 2005), there are a magnitude of other spatiotemporal parameters describing gait that have also been related to fall risk. Based on this limited prior work, it was hypothesized that increased levels of SAA would be related to decreased gait speed and increased temporal variability, especially when walking with a concurrent cognitive task.

Two different analyses were conducted to better understand what impacts SAA may have on spatiotemporal characteristics of gait. First, the Pearson correlation coefficient was calculated between all five gait measures within all three tasks and SAA. It was determined that no significant relationships existed between SAA and spatiotemporal parameters of gait, regardless of task condition. These results remained consistent even when adjusting for average gait speed during the task of interest. The second analysis was conducted using the R^2 difference between each predictor variable regressed on gait speed alone and then with both gait speed and the temporal variability parameter of interest. According to Kang and Dingwell (2007), gait variability varies with walking speed. In older adults, this poses an issue in identifying the underlying cause of changes, more specifically increases, in gait variability due to their typical decreases in walking speeds. Through the statistical model used, the data could be further explored to understand if the reason for changes in variability was actually due to changes in walking speed or some other confounding effects such as SAA level. Seven of the fifteen regressions involving SAA across all tasks and temporal gait parameters provided a significant result indicating that SAA significantly contributed to the variability in the selected parameters above and beyond that explained by average GS. The largest contribution of SAA was its contribution of 4% to the variability in stance time variability during a B task above and beyond

that of average GS. There were no significant findings with variability in cadence variability. However, the average across all significant findings was very small with only 1.9% contribution to variability.

The lack of correlation between SAA and spatiotemporal gait characteristics and the minimal contribution of SAA to the variability in temporal variability above and beyond that of gait speed suggest that the variability in temporal variability parameters is not under the direct influence of SAA, and that there must be some other underlying cause for any changes in variability. Gait speed was not directly correlated with SAA. These results do not support previous work concluding that increased SAA is associated with a decrease in gait speed (Nebes et al., 2007; Cao et al., 2008). However, gait speed could be one of the major contributors causing the changes in gait variability measures. The average R^2 value for only gait speed in the model with each of the temporal variability parameters was 0.17 with a maximum of 0.414. The largest R^2 values were seen with stance time variability. This can be interpreted as the largest known contribution accounting for the variability in temporal variability for these participants may actually be gait speed, not SAA. Additionally, pilot work conducted prior to the beginning of this research project found increased stride time variability with increased SAA during dual-task walking. While stride time variability was not calculated for this project, it could be concluded that SAA has previously demonstrated some impact on gait variability.

While the underlying cause for changes in variability are unclear from this analysis, the lack of significance may again be related to overall participant health. For this analysis, the average SAA was slightly less at 0.50 pmole mL atropine equivalent^{-1} with range of 0-2.05 pmole mL atropine equivalent^{-1}. Previous work has quantified SAA in the same manner as done here, and these results are presented in Section 4.1.2. Comparatively, our participants again have

a very low average SAA level and very small variance. If SAA levels were to be higher in this population with a larger variance, we would have expected to see some relationships between variability and SAA and a larger contribution of SAA to the variability above and beyond that explained by average GS. This theory stems from one of the main actions of anticholinergic medications in its impact on cognition and attention. As previously mentioned, walking while performing a concurrent task involves continuous competition for available resources. Specifically, the attention demands of both tasks competing for the limited attention capacity could lead to degradation in one or both tasks (Abernethy, 1988; Pashler, 1994; Beauchet & Berrut, 2006). If anticholinergics are indeed capable of modifying or limiting the capacity of attention, the demands of both tasks will be competing for an even more limited amount of attention. As a result, there should be even more significant changes in gait variability (i.e. increased variability) and poorer performance on the cognitive challenge task.

4.2.3 Spatiotemporal Gait Characteristics and WMH

The second half of Specific Aim 2 was to investigate the relationship between WMH and spatiotemporal gait during single-task walking and walking under a dual-task. While the exact mechanism of action is unclear, previous work has been done to quantify gait characteristics and related them to WMH. Results of this work showed decreased gait speed, increased stride time, and increased double support time with increased WMH (Rosano et al., 2006; Murray et al., 2010). With this, it was hypothesized that with increasing WMH, we would also expect to see decreased gait speed but also increased temporal variability. This was tested using two different analyses. We first used the Pearson correlation coefficient to identify any relationships between gait and WMH across all tasks. Our results showed that none of the spatiotemporal gait

characteristics were correlated with WMH. We then repeated this analysis by adjusting for gait speed and this time found one significant correlation between STV and SS during the F task. However, since this was the only correlation present out of 48 (0.02%), it may actually be due to chance or noise within the model that this significant relationship was shown. These results do not agree with previous literature.

The second analysis was performed to understand the contributions of average GS and the predictor variables to the variability in temporal variability. Several significant contributions of WMH and WMH in the regions of interest were identified except for in cadence variability. But, just as in the SAA analysis, the contribution of WMH to the variability of temporal variability above and beyond that of average GS was quite small. The average contribution was only 2.56% with a range from 0-11%. Moreover, average GS had an average contribution to temporal variability of 25.3% with a range of 15-33%. It is difficult to conclude that WMH truly contributed a significant amount to temporal variability when the percentage was so small.

These results demonstrate that temporal variability is not under the direct control of overall WMH or the WMH within the regions of interest selected. While the contributions of WMH to the overall variability in temporal variability were significant for a sub-set of variables, the actual values of these contributions were very small. From these results, several conclusions can be made. First, with respect to this analysis, it appears that gait speed is the largest factor affecting variability. This conclusion is in support of work by Kang and Dingwell (2007). By modulating gait speed throughout the duration of the 60 second walking trial and between trials, it makes sense that participants would become more variable in the number of steps taken, the time each foot is on the ground, and the timing between steps. Second, the participants in this analysis did demonstrate temporal variability not fully explained by gait speed. Some other

underlying factor must be causing these changes. While it is unclear based on the metrics obtained in this population, it can be proposed that other aspects inherent with aging including the adoption of cautious gait and the fear of falling (Hausdorff et al., 2001; Menz et al., 2003) may be the cause of the changes in temporal variability seen here. Third, as mentioned throughout this work, the overall health status of the participant population used may have limited the results obtained. Work by others measuring WMH in the same manner as conducted here was presented in section 4.1.2. For this analysis, the average overall WMH was very small at 0.112% total brain volume with an additionally small range of 0.00555-0.452% total brain volume. Without a larger magnitude and variance of WMH within the population recruited, it may be that the participants did not actually experience the adverse effects associated with WMH such as demyelination, loss of axons, gliosis, and dilation of the periventricular space have all been associated with WMH (Ota et al., 2010). Without these physiological barriers impacting the neural health of our participants, it can be further supported that WMH did not cause the changes seen here in temporal variability.

4.2.4 Spatiotemporal Gait Characteristics and the Combined Effects of SAA and WMH

The second half of Specific Aim 3 looked to determine if there was a relationship between spatiotemporal characteristics under different task conditions with the combined effects of SAA and WMH. As was done with the balance outcome measures, this was accomplished using the volume of WMH located in the CHOL and NON-CHOL tracts as determined by MRI. Again, CHOL are the tracts containing cholinergic fibers while NON-CHOL are the tracts not containing cholinergic fibers. It was hypothesized that participants taking anticholinergic medications who also showed the presence of WMH within the cholinergic tracts would have

increased temporal variability, and this increase would be exaggerated with performing a dual-task. Using the Pearson correlation, our results indicate that there were four significant correlations between temporal variability and WMH when not adjusted for gait speed and only three significant correlations when adjusted for gait speed. These significant findings occurred during NT conditions in STV, SEV, and CV. However, these findings do not support the hypothesis that spatiotemporal gait parameters are affected by the combined interaction of SAA and WMH since the findings were not the in the tracts containing cholinergic fibers. When looking at the contribution of CHOL to the variability in temporal variability above and beyond that explained by gait speed, there were no significant contributions of CHOL to the variability of temporal variability above and beyond that attributed to gait speed. While there were some significant findings with NON-CHOL, these findings can be considered comparable to those of WMH as the non-cholinergic tracts are simply measures of WMH without the presence of cholinergic fibers.

Under these findings, it can be concluded that there were no significant relationships between the combined interaction effects of WMH and SAA on temporal variability. This conclusion does not come as a surprise. To have seen results in this analysis, we would have expected to also see significant relationships of SAA and WMH with temporal variability or at least major contributions of SAA and WMH to temporal variability. These relationships were not found given the participant sample studied in this analysis. Without significant WMH, the effects of anticholinergic medications are not enhanced as would be in the presence of greater WMH. It is important to note that for this analysis, six of the 20 participants did not even have detectable WMH in the cholinergic tracts. Without the presence of WMH in the tract of interest, the correlation analysis is extremely limited. Again, as previously stated, the participants selected for

this study were extremely healthy with limited presence of WMH and very low levels of SAA. Without a large variance of the predictor variables of interest, it is not surprising that the results were very limited.

5.0 LIMITATIONS

5.1 PARTICIPANT CHARACTERISTICS

The statistical significance of this study may have been compromised due to the lack of large variance of predictor variables such as SAA and overall WMH. The screening process for participant recruitment was designed to ensure that participants would not be at risk during participation in the research protocol, did not have any known conditions that would prevent them from standing or walking normally, and did not have any neural changes such as known depression or cognitive deficit to interfere with the success of the dual-task. While it is important to eliminate these participants from testing if it would be a risk to their safety or if they could not perform the tasks, it may be of importance to consider a wider range participants based on certain criteria such as medication use. By recruiting participants with a higher chance of exhibiting the characteristics of interest such as known anticholinergic use, the results from future work with this protocol may show significant findings.

5.2 TESTING AREA

While participants were capable of walking for a continuous 60 seconds during each walking trial, participants were required to walk on a small, tight circular track to maintain this

continuous path. The Vicon motion capture system is limited in the volume of space at which it is capable of capturing motion, resulting in tight turns at the end of each straightaway for participants to navigate in order to maximize time walked on the straight portion of the track. While data was not processed when captured over the turns, participants may have altered their gait approximately two steps prior to and after the turns in order to safely navigate them. This may have then impacted temporal variability within the straightaways if the participants were not able to recover from the alterations made within the turn. It would be ideal if this study could be conducted using an instrumented treadmill or shorter protocol duration in a larger room that would allow for continuous, straight walking.

6.0 CONCLUSION

The purpose of this research project was to determine whether balance or gait are negatively affected by the use of anticholinergic medications, white matter hyperintensities in the brain, and the combined effects of both in older adults during single and dual-task conditions. Results from this study indicate that there is not a direct relationship between the use of anticholinergic medications and the aging of the brain indicated by WMH to balance or gait, regardless of task condition. Additionally, the combined effects of WMH and anticholinergic medications were also not found to be significantly related to balance or gait, regardless of task. While some significant relationships were found, the magnitude of relationships investigated to the actual number of findings is so much larger that the significant findings are not enough to provide conclusive results. However, findings from this study did confirm several previous works by other authors that balance and gait suffer when performed under a dual-task, independent of anticholinergic burden and WMH. There was a decline is overall balance performance, decrease in gait speed, and increase in temporal variability, putting all of the participants of this study at an increased risk for falls when either attempting to maintain balance or walking normally while performing a secondary cognitive task. From this, it can be concluded that while WMH and SAA are not the direct causes of changes in balance or walking performance in the participants used for this analysis, other factors relative to aging including changes in muscular strength, gait

speed and fear of falling may be linked to the changes that were seen in the balance and gait measures.

While the anticipated relationships were not found and limitations of this study exist, this work still provides implications for future studies to investigate possible relationships between anticholinergic medications and WMH. By recruiting participants based on medication use or known MRI findings, a larger variance of predictor variables may allow for relationships between the variables of interest to be determined. By better understanding these relationships and being able to link changes in balance and gait to specific neural regions of interest and quantified medication burden, we may be one step closer to understanding the mechanism of action on physical function by the predictor variables. Once this is understood, better care can be taken to monitor medication use and provide therapeutic training to people at a higher risk for falls as related to medication burden and changes in WMH with age.

APPENDIX A

BALANCE RESULTS

Table 17: Unadjusted and Adjusted Spearman correlation coefficients and their corresponding p-values describing the relationship between the COP variables of interest and CHOL, NON-CHOL, SAA, WMH ALL, AACC, SS, and CC (α=0.05) for EC and EO conditions and all tasks. Significance is denoted by an asterisk (*).

Eye	Task	COP	Predictor Variable	Unadjusted Spearman Coefficient	Unadjusted Spearman p-value	Adjusted Spearman Coefficient	Adjusted Spearman p-value
EO	NT	AP RMS	CHOL	0.053	0.82	0.032	0.89
EO	NT	AP RMS	NON-CHOL	0.36	0.11	0.31	0.19
EO	NT	AP RMS	SAA	-0.20	0.18	-0.21	0.18
EO	NT	AP RMS	WMH ALL	0.28	0.096	0.32	0.063
EO	NT	AP RMS	AACC	0.10	0.56	0.14	0.43
EO	NT	AP RMS	CC	0.33	0.052	0.38	0.026 *
EO	NT	AP RMS	SS	0.0045	0.98	0.017	0.92
EO	NT	ML RMS	CHOL	-0.11	0.64	-0.16	0.49

Table 17 (continued)

EO	NT	ML RMS	NON-CHOL	-0.023	0.92	-0.16	0.49
EO	NT	ML RMS	SAA	-0.15	0.34	-0.14	0.37
EO	NT	ML RMS	WMH ALL	0.051	0.77	0.11	0.54
EO	NT	ML RMS	AACC	-0.074	0.67	-0.014	0.94
EO	NT	ML RMS	CC	0.14	0.41	0.22	0.21
EO	NT	ML RMS	SS	-0.023	0.89	0.0012	0.99
EO	NT	PL	CHOL	0.12	0.59	0.10	0.67
EO	NT	PL	NON-CHOL	-0.025	0.92	-0.13	0.57
EO	NT	PL	SAA	-0.12	0.43	-0.11	0.49
EO	NT	PL	WMH ALL	-0.063	0.71	0.015	0.93
EO	NT	PL	AACC	-0.17	0.32	-0.087	0.62
EO	NT	PL	CC	0.081	0.64	0.19	0.26
EO	NT	PL	SS	-0.17	0.33	-0.14	0.42
EO	NT	AP VEL	CHOL	0.13	0.57	0.11	0.63
EO	NT	AP VEL	NON-CHOL	0.029	0.99	-0.063	0.79
EO	NT	AP VEL	SAA	-0.16	0.31	-0.15	0.35
EO	NT	AP VEL	WMH ALL	-0.21	0.23	-0.14	0.41
EO	NT	AP VEL	AACC	-0.23	0.18	-0.15	0.38
EO	NT	AP VEL	CC	-0.066	0.70	0.027	0.88
EO	NT	AP VEL	SS	-0.16	0.35	-0.13	0.44
EO	NT	ML VEL	CHOL	0.14	0.53	0.13	0.58
EO	NT	ML VEL	NON-CHOL	-0.10	0.66	-0.17	0.46
EO	NT	ML VEL	SAA	-0.11	0.47	-0.098	0.53

Table 17 (continued)

EO	NT	ML VEL	WMH ALL	0.12	0.49	0.19	0.27
EO	NT	ML VEL	AACC	-0.056	0.75	0.019	0.91
EO	NT	ML VEL	CC	0.25	0.15	0.35	0.041 *
EO	NT	ML VEL	SS	-0.11	0.52	-0.087	0.62
EO	F	AP RMS	CHOL	0.22	0.34	0.21	0.37
EO	F	AP RMS	NON-CHOL	0.16	0.50	0.14	0.57
EO	F	AP RMS	SAA	-0.10	0.51	-0.099	0.52
EO	F	AP RMS	WMH ALL	0.12	0.47	0.13	0.46
EO	F	AP RMS	AACC	0.12	0.49	0.12	0.48
EO	F	AP RMS	CC	0.18	0.31	0.18	0.29
EO	F	AP RMS	SS	-0.13	0.44	-0.13	0.45
EO	F	ML RMS	CHOL	-0.029	0.90	-0.051	0.83
EO	F	ML RMS	NON-CHOL	0.32	0.16	0.27	0.25
EO	F	ML RMS	SAA	-0.016	0.92	-0.0073	0.96
EO	F	ML RMS	WMH ALL	0.11	0.54	0.13	0.45
EO	F	ML RMS	AACC	0.079	0.64	0.11	0.52
EO	F	ML RMS	CC	0.14	0.40	0.18	0.30
EO	F	ML RMS	SS	-0.028	0.87	-0.018	0.92
EO	F	PL	CHOL	0.14	0.55	0.14	0.55
EO	F	PL	NON-CHOL	0.065	0.78	0.082	0.73
EO	F	PL	SAA	0.069	0.66	0.082	0.60

Table 17 (continued)

EO	F	PL	WMH ALL	0.038	0.83	0.067	0.70
EO	F	PL	AACC	-0.021	0.91	0.013	0.94
EO	F	PL	CC	0.168	0.33	0.21	0.22
EO	F	PL	SS	-0.16	0.34	-0.15	0.38
EO	F	AP VEL	CHOL	0.24	0.29	0.25	0.30
EO	F	AP VEL	NON-CHOL	0.079	0.73	0.10	0.67
EO	F	AP VEL	SAA	0.068	0.66	0.083	0.60
EO	F	AP VEL	WMH ALL	-0.027	0.88	0.0064	0.97
EO	F	AP VEL	AACC	-0.062	0.72	-0.024	0.89
EO	F	AP VEL	CC	0.079	0.65	0.13	0.47
EO	F	AP VEL	SS	-0.23	0.18	-0.22	0.21
EO	F	ML VEL	CHOL	0.013	0.96	0.017	0.94
EO	F	ML VEL	NON-CHOL	-0.0078	0.97	0.0054	0.98
EO	F	ML VEL	SAA	0.043	0.78	0.05	0.75
EO	F	ML VEL	WMH ALL	0.17	0.33	0.18	0.30
EO	F	ML VEL	AACC	0.086	0.62	0.098	0.57
EO	F	ML VEL	CC	0.28	0.093	0.31	0.074
EO	F	ML VEL	SS	-0.0022	0.99	0.0011	0.99
EO	B	AP RMS	CHOL	0.0040	0.99	-0.015	0.95
EO	B	AP RMS	NON-CHOL	0.15	0.53	0.091	0.70
EO	B	AP RMS	SAA	-0.14	0.39	-0.13	0.42
EO	B	AP RMS	WMH ALL	-0.027	0.88	0.028	0.88

Table 17 (continued)

EO	B	AP RMS	AACC	-0.10	0.56	-0.042	0.81
EO	B	AP RMS	CC	0.047	0.79	0.13	0.47
EO	B	AP RMS	SS	-0.082	0.64	-0.059	0.74
EO	B	ML RMS	CHOL	0.16	0.49	0.14	0.56
EO	B	ML RMS	NON-CHOL	0.22	0.34	0.13	0.58
EO	B	ML RMS	SAA	-0.25	0.10	-0.24	0.12
EO	B	ML RMS	WMH ALL	0.030	0.86	0.10	0.57
EO	B	ML RMS	AACC	-0.0066	0.97	0.076	0.67
EO	B	ML RMS	CC	0.13	0.45	0.24	0.17
EO	B	ML RMS	SS	-0.23	0.19	-0.21	0.24
EO	B	PL	CHOL	0.094	0.68	0.085	0.72
EO	B	PL	NON-CHOL	-0.10	0.66	-0.14	0.55
EO	B	PL	SAA	-0.076	0.63	-0.060	0.71
EO	B	PL	WMH ALL	-0.16	0.37	-0.096	0.59
EO	B	PL	AACC	-0.22	0.20	-0.16	0.38
EO	B	PL	CC	-0.030	0.86	0.063	0.73
EO	B	PL	SS	-0.24	0.16	-0.22	0.21
EO	B	AP VEL	CHOL	0.12	0.60	0.11	0.63
EO	B	AP VEL	NON-CHOL	-0.0078	0.97	-0.037	0.88
EO	B	AP VEL	SAA	-0.041	0.80	-0.016	0.92
EO	B	AP VEL	WMH ALL	-0.18	0.29	-0.12	0.49
EO	B	AP VEL	AACC	-0.22	0.21	-0.15	0.41
EO	B	AP VEL	CC	-0.058	0.74	0.037	0.83

Table 17 (continued)

EO	B	AP VEL	SS	-0.30	0.085	-0.28	0.11
EO	B	ML VEL	CHOL	0.15	0.52	0.15	0.53
EO	B	ML VEL	NON-CHOL	-0.19	0.42	-0.19	0.41
EO	B	ML VEL	SAA	-0.069	0.66	-0.063	0.69
EO	B	ML VEL	WMH ALL	0.017	0.92	0.048	0.79
EO	B	ML VEL	AACC	-0.083	0.64	-0.051	0.77
EO	B	ML VEL	CC	0.14	0.42	0.19	0.28
EO	B	ML VEL	SS	-0.17	0.34	-0.15	0.38
EC	NT	AP RMS	CHOL	-0.28	0.21	-0.33	0.16
EC	NT	AP RMS	NON-CHOL	0.41	0.068	0.35	0.13
EC	NT	AP RMS	SAA	0.097	0.53	0.11	0.49
EC	NT	AP RMS	WMH ALL	0.31	0.068	0.36	0.034 *
EC	NT	AP RMS	AACC	0.23	0.18	0.24	0.18
EC	NT	AP RMS	CC	0.19	0.27	0.22	0.21
EC	NT	AP RMS	SS	0.43	0.011 *	0.46	0.0061 *
EC	NT	ML RMS	CHOL	0.10	0.66	0.096	0.69
EC	NT	ML RMS	NON-CHOL	0.25	0.27	0.23	0.32
EC	NT	ML RMS	SAA	-0.095	0.54	-0.092	0.56
EC	NT	ML RMS	WMH ALL	0.42	0.011 *	0.45	0.0063 *
EC	NT	ML RMS	AACC	0.34	0.045 *	0.39	0.022 *
EC	NT	ML RMS	CC	0.45	0.0057 *	0.51	0.0023 *

Table 17 (continued)

EC	NT	ML RMS	SS	0.21	0.24	0.23	0.20
EC	NT	PL	CHOL	0.065	0.78	0.059	0.80
EC	NT	PL	NON-CHOL	0.031	0.89	0.0089	0.97
EC	NT	PL	SAA	-0.088	0.57	-0.078	0.62
EC	NT	PL	WMH ALL	0.11	0.52	0.14	0.41
EC	NT	PL	AACC	0.027	0.87	0.12	0.51
EC	NT	PL	CC	0.21	0.23	0.28	0.10
EC	NT	PL	SS	0.070	0.69	0.11	0.55
EC	NT	AP VEL	CHOL	0.14	0.53	0.13	0.57
EC	NT	AP VEL	NON-CHOL	0.058	0.80	0.019	0.94
EC	NT	AP VEL	SAA	-0.12	0.45	-0.11	0.49
EC	NT	AP VEL	WMH ALL	-0.037	0.83	-0.0037	0.98
EC	NT	AP VEL	AACC	-0.10	0.55	-0.011	0.95
EC	NT	AP VEL	CC	0.059	0.73	0.14	0.43
EC	NT	AP VEL	SS	-0.11	0.53	-0.074	0.68
EC	NT	ML VEL	CHOL	0.093	0.69	0.10	0.68
EC	NT	ML VEL	NON-CHOL	-0.012	0.96	0.0092	0.97
EC	NT	ML VEL	SAA	-0.0073	0.96	-0.00065	0.99
EC	NT	ML VEL	WMH ALL	0.29	0.086	0.30	0.085
EC	NT	ML VEL	AACC	0.17	0.31	0.23	0.20
EC	NT	ML VEL	CC	0.38	0.022 *	0.43	0.012 *
EC	NT	ML VEL	SS	0.26	0.14	0.27	0.12
EC	F	AP RMS	CHOL	0.13	0.59	0.10	0.67

Table 17 (continued)

EC	F	AP RMS	NON-CHOL	0.29	0.19	0.20	0.40
EC	F	AP RMS	SAA	-0.053	0.73	-0.035	0.82
EC	F	AP RMS	WMH ALL	0.27	0.11	0.37	0.031 *
EC	F	AP RMS	AACC	0.16	0.34	0.24	0.16
EC	F	AP RMS	CC	0.30	0.080	0.39	0.023 *
EC	F	AP RMS	SS	0.23	0.19	0.30	0.086
EC	F	ML RMS	CHOL	0.0040	0.99	-0.031	0.90
EC	F	ML RMS	NON-CHOL	0.021	0.93	-0.098	0.68
EC	F	ML RMS	SAA	-0.18	0.25	-0.17	0.29
EC	F	ML RMS	WMH ALL	0.13	0.46	0.16	0.35
EC	F	ML RMS	AACC	0.11	0.51	0.24	0.17
EC	F	ML RMS	CC	0.18	0.30	0.27	0.12
EC	F	ML RMS	SS	0.30	0.082	0.35	0.041 *
EC	F	PL	CHOL	0.14	0.55	0.12	0.60
EC	F	PL	NON-CHOL	0.0026	0.99	-0.055	0.82
EC	F	PL	SAA	-0.16	0.31	-0.15	0.34
EC	F	PL	WMH ALL	0.11	0.54	0.13	0.47
EC	F	PL	AACC	0.050	0.77	0.15	0.40
EC	F	PL	CC	0.22	0.20	0.30	0.008
EC	F	PL	SS	0.16	0.37	0.19	0.29
EC	F	AP VEL	CHOL	0.089	0.70	0.074	0.76
EC	F	AP VEL	NON-CHOL	0.053	0.82	-0.020	0.99
EC	F	AP VEL	SAA	-0.099	0.52	-0.089	0.57

Table 17 (continued)

EC	F	AP VEL	WMH ALL	0.11	0.51	0.14	0.42
EC	F	AP VEL	AACC	0.047	0.79	0.15	0.49
EC	F	AP VEL	CC	0.23	0.17	0.31	0.071
EC	F	AP VEL	SS	0.11	0.52	0.15	0.41
EC	F	ML VEL	CHOL	0.067	0.87	0.054	0.82
EC	F	ML VEL	NON-CHOL	-0.039	0.867	-0.089	0.71
EC	F	ML VEL	SAA	-0.17	0.28	-0.16	0.30
EC	F	ML VEL	WMH ALL	0.16	0.36	0.16	0.35
EC	F	ML VEL	AACC	0.11	0.53	0.17	0.34
EC	F	ML VEL	CC	0.24	0.16	0.28	0.10
EC	F	ML VEL	SS	0.20	0.26	0.21	0.23
EC	B	AP RMS	CHOL	0.080	0.73	0.066	0.78
EC	B	AP RMS	NON-CHOL	0.082	0.72	0.033	0.89
EC	B	AP RMS	SAA	-0.19	0.90	-0.0085	0.96
EC	B	AP RMS	WMH ALL	-0.046	0.79	0.016	0.93
EC	B	AP RMS	AACC	-0.075	0.67	0.083	0.64
EC	B	AP RMS	CC	0.020	0.91	0.16	0.38
EC	B	AP RMS	SS	-0.056	0.75	0.011	0.95
EC	B	ML RMS	CHOL	0.24	0.30	0.24	0.31
EC	B	ML RMS	NON-CHOL	0.034	0.88	0.024	0.92
EC	B	ML RMS	SAA	-0.15	0.32	-0.15	0.33

Table 17 (continued)

EC	B	ML RMS	WMH ALL	0.11	0.51	0.13	0.45
EC	B	ML RMS	AACC	0.0041	0.98	0.10	0.56
EC	B	ML RMS	CC	0.22	0.20	0.31	0.076
EC	B	ML RMS	SS	0.043	0.81	0.075	0.67
EC	B	PL	CHOL	0.082	0.72	0.074	0.76
EC	B	PL	NON-CHOL	0.0052	0.98	-0.027	0.91
EC	B	PL	SAA	-0.15	0.34	-0.14	0.38
EC	B	PL	WMH ALL	-0.070	0.69	-0.037	0.83
EC	B	PL	AACC	-0.13	0.45	-0.035	0.84
EC	B	PL	CC	0.069	0.69	0.15	0.39
EC	B	PL	SS	-0.078	0.65	-0.038	0.83
EC	B	AP VEL	CHOL	0.11	0.62	0.10	0.66
EC	B	AP VEL	NON-CHOL	0.027	0.91	-0.016	0.95
EC	B	AP VEL	SAA	-0.10	0.50	-0.091	0.56
EC	B	AP VEL	WMH ALL	-0.14	0.41	-0.10	0.56
EC	B	AP VEL	AACC	-0.19	0.26	-0.094	0.60
EC	B	AP VEL	CC	0.0093	0.96	0.095	0.59
EC	B	AP VEL	SS	-0.12	0.50	-0.076	0.67
EC	B	ML VEL	CHOL	0.13	0.58	0.12	0.60
EC	B	ML VEL	NON-CHOL	0.043	0.85	0.026	0.91
EC	B	ML VEL	SAA	-0.17	0.28	-0.16	0.31
EC	B	ML VEL	WMH ALL	0.044	0.8	0.069	0.69
EC	B	ML VEL	AACC	-0.038	0.83	0.025	0.89

Table 17 (continued)

EC	B	ML VEL	CC	0.15	0.39	0.20	0.25
EC	B	ML VEL	SS	-0.013	0.94	0.017	0.93

APPENDIX B

GAIT RESULTS

Table 18: Unadjusted and adjusted Pearson correlation coefficients and their corresponding p-values describing the relationship between Average GS, the gait variability variables of interest and CHOL, NON-CHOL, SAA, WMH ALL, AACC, SS, and CC (α=0.05) for all tasks. Significance is denoted by an asterisk (*).

Task	Variability Measure	Predictor Variable	Unadjusted Pearson Coefficient	Unadjusted Pearson p-value	Adjusted Pearson Coefficient	Adjusted Pearson p-value
NT	Average GS	CHOL	-0.022	0.93	--	--
NT	Average GS	NON-CHOL	-0.22	0.36	--	--
NT	Average GS	SAA	0.22	0.17	--	--
NT	Average GS	WMH ALL	0.10	0.58	--	--
NT	Average GS	AACC	0.16	0.37	--	--
NT	Average GS	CC	0.11	0.53	--	--
NT	Average GS	SS	0.016	0.93	--	--
F	Average GS	CHOL	0.028	0.91	--	--
F	Average GS	NON-CHOL	-0.19	0.41	--	--
F	Average GS	SAA	0.20	0.22	--	--
F	Average GS	WMH ALL	0.10	0.57	--	--
F	Average GS	AACC	0.16	0.39	--	--

Table 18 (continued)

F	Average GS	CC	0.11	0.54	--	--
F	Average GS	SS	0.019	0.91	--	--
B	Average GS	CHOL	-0.078	0.74	--	--
B	Average GS	NON-CHOL	-0.27	0.26	--	--
B	Average GS	SAA	0.082	0.61	--	--
B	Average GS	WMH ALL	0.095	0.61	--	--
B	Average GS	AACC	0.16	0.37	--	--
B	Average GS	CC	0.078	0.67	--	--
B	Average GS	SS	0.032	0.86	--	--
NT	CV	CHOL	0.15	0.53	0.15	0.54
NT	CV	NON-CHOL	0.56	0.01 *	0.56	0.012 *
NT	CV	SAA	0.071	0.66	0.093	0.58
NT	CV	WMH ALL	0.19	0.27	0.20	0.26
NT	CV	AACC	0.062	0.74	0.076	0.69
NT	CV	CC	0.22	0.23	0.23	0.21
NT	CV	SS	0.095	0.61	0.096	0.61
F	CV	CHOL	0.16	0.50	0.16	0.51
F	CV	NON-CHOL	-0.024	0.92	-0.027	0.91
F	CV	SAA	-0.12	0.47	-0.12	0.49
F	CV	WMH ALL	0.010	0.96	0.016	0.93
F	CV	AACC	-0.0048	0.98	0.0083	0.96
F	CV	CC	0.14	0.44	0.15	0.41
F	CV	SS	0.037	0.84	0.039	0.83
B	CV	CHOL	0.19	0.43	0.19	0.43
B	CV	NON-CHOL	0.16	0.49	0.19	0.45
B	CV	SAA	0.029	0.86	0.028	0.87
B	CV	WMH ALL	0.093	0.60	0.10	0.57
B	CV	AACC	0.0088	0.96	0.031	0.87
B	CV	CC	0.19	0.30	0.20	0.28
B	CV	SS	0.042	0.82	0.046	0.81
NT	DSV	CHOL	-0.0039	0.99	-0.016	0.95

Table 18 (continued)

NT	DSV	NON-CHOL	0.94	0.084	0.34	0.15
NT	DSV	SAA	0.060	0.71	0.19	0.25
NT	DSV	WMH ALL	0.17	0.34	0.23	0.20
NT	DSV	AACC	0.077	0.68	0.15	0.42
NT	DSV	CC	0.22	0.22	0.29	0.12
NT	DSV	SS	-0.021	0.91	-0.016	0.93
F	DSV	CHOL	0.090	0.71	0.10	0.68
F	DSV	NON-CHOL	-0.055	0.82	-0.11	0.65
F	DSV	SAA	-0.098	0.55	-0.041	0.81
F	DSV	WMH ALL	0.033	0.85	0.066	0.72
F	DSV	AACC	0.0062	0.97	0.052	0.78
F	DSV	CC	0.16	0.38	0.20	0.28
F	DSV	SS	0.070	0.70	0.079	0.67
B	DSV	CHOL	0.16	0.51	0.15	0.54
B	DSV	NON-CHOL	0.11	0.64	0.074	0.76
B	DSV	SAA	-0.021	0.90	0.00021	0.99
B	DSV	WMH ALL	0.15	0.41	0.18	0.33
B	DSV	AACC	0.036	0.85	0.082	0.66
B	DSV	CC	0.25	0.17	0.28	0.13
B	DSV	SS	0.063	0.73	0.073	0.70
NT	STV	CHOL	0.074	0.76	0.076	0.76
NT	STV	NON-CHOL	0.58	0.0075 *	0.57	0.010 *
NT	STV	SAA	-0.095	0.56	0.063	0.70
NT	STV	WMH ALL	0.14	0.44	0.26	0.15
NT	STV	AACC	0.081	0.66	0.23	0.22
NT	STV	CC	0.14	0.44	0.26	0.15
NT	STV	SS	0.053	0.77	0.077	0.68
F	STV	CHOL	0.17	0.47	0.21	0.40
F	STV	NON-CHOL	0.046	0.85	-0.046	0.85
F	STV	SAA	-0.28	0.084	-0.21	0.20

Table 18 (continued)

F	STV	WMH ALL	0.046	0.80	0.11	0.54
F	STV	AACC	0.056	0.76	0.15	0.43
F	STV	CC	0.091	0.62	0.16	0.39
F	STV	SS	0.32	0.070	0.37	0.038 *
B	STV	CHOL	0.19	0.42	0.18	0.47
B	STV	NON-CHOL	0.35	0.13	0.26	0.29
B	STV	SAA	0.013	0.94	0.073	0.66
B	STV	WMH ALL	0.13	0.48	0.23	0.20
B	STV	AACC	0.022	0.91	0.14	0.44
B	STV	CC	0.21	0.25	0.31	0.090
B	STV	SS	0.023	0.90	0.051	0.79
NT	SEV	CHOL	0.030	0.90	0.022	0.93
NT	SEV	NON-CHOL	0.49	0.027 *	0.45	0.051
NT	SEV	SAA	-0.078	0.63	0.038	0.82
NT	SEV	WMH ALL	0.087	0.63	0.16	0.38
NT	SEV	AACC	-0.0093	0.96	0.075	0.69
NT	SEV	CC	0.098	0.59	0.17	0.36
NT	SEV	SS	0.12	0.50	0.15	0.43
F	SEV	CHOL	0.15	0.53	0.19	0.44
F	SEV	NON-CHOL	0.10	0.67	0.010	0.97
F	SEV	SAA	-0.17	0.29	-0.10	0.56
F	SEV	WMH ALL	-0.047	0.80	0.0057	0.98
F	SEV	AACC	-0.0043	0.98	0.077	0.69
F	SEV	CC	-0.027	0.89	0.029	0.88
F	SEV	SS	0.21	0.25	0.25	0.18
B	SEV	CHOL	0.31	0.19	0.31	0.21
B	SEV	NON-CHOL	0.58	0.0088 *	0.54	0.021 *
B	SEV	SAA	0.11	0.51	0.17	0.31
B	SEV	WMH ALL	0.099	0.59	0.18	0.33
B	SEV	AACC	0.023	0.90	0.14	0.47
B	SEV	CC	0.088	0.64	0.15	0.42
B	SEV	SS	0.18	0.34	0.23	0.21

Table 19: R^2 values obtained by regressing each gait variability measure on average GS alone (A), each predictor variable only (B), and on average GS and each predictor variable combined (C). The added value of each predictor variable is quantified using the R^2 difference between models C and A. Statistical significance of the combined effects was set at $\alpha=0.05$ and is denoted by an asterisk.

Task	Variability Measure	Predictor Variable	GS Only (A)	Predictor Only (B)	GS & Predictor (C)	ΔR^2 (C-A)	p-value of ΔR^2
NT	CV	CHOL	0.0037	0.022	0.026	0.022	0.80
NT	CV	NON-CHOL	0.0037	0.32	0.32	0.32	0.038 *
NT	CV	SAA	0.0072	0.0051	0.016	0.0088	0.75
NT	CV	WMH ALL	0.0074	0.037	0.049	0.042	0.46
NT	CV	AACC	0.0074	0.008	0.019	0.012	0.74
NT	CV	CC	0.0074	0.054	0.069	0.062	0.33
NT	CV	SS	0.0057	0.0089	0.015	0.0093	0.81
F	CV	CHOL	0.0002	0.026	0.026	0.026	0.80
F	CV	NON-CHOL	0.0002	0.0006	0.0009	0.0007	0.99
F	CV	SAA	0.0005	0.014	0.014	0.014	0.77
F	CV	WMH ALL	0.002	0.0001	0.0022	0.0002	0.97
F	CV	AACC	0.002	0.0001	0.002	0	0.97
F	CV	CC	0.002	0.018	0.022	0.02	0.71
F	CV	SS	0.0068	0.0014	0.0082	0.0014	0.88
B	CV	CHOL	0.0036	0.035	0.040	0.036	0.71
B	CV	NON-CHOL	0.0036	0.026	0.038	0.034	0.72
B	CV	SAA	0.0003	0.0008	0.0011	0.0008	0.98
B	CV	WMH ALL	0.0063	0.0087	0.017	0.011	0.77
B	CV	AACC	0.0063	0.0008	0.0083	0.002	0.88
B	CV	CC	0.0063	0.039	0.05	0.044	0.45
B	CV	SS	0.0173	0.0017	0.019	0.0017	0.75
NT	DSV	CHOL	0.22	0	0.22	0	0.12
NT	DSV	NON-CHOL	0.22	0.156	0.31	0.09	0.042 *

Table 19 (continued)

NT	DSV	SAA	0.22	0.0036	0.25	0.03	0.0054 *
NT	DSV	WMH ALL	0.15	0.028	0.20	0.05	0.034 *
NT	DSV	AACC	0.15	0.0016	0.17	0.02	0.061
NT	DSV	CC	0.15	0.033	0.21	0.06	0.026 *
NT	DSV	SS	0.14	0.0004	0.14	0	0.11
F	DSV	CHOL	0.067	0.0081	0.077	0.01	0.51
F	DSV	NON-CHOL	0.067	0.003	0.079	0.012	0.50
F	DSV	SAA	0.092	0.0096	0.093	0.001	0.16
F	DSV	WMH ALL	0.063	0.0011	0.067	0.004	0.34
F	DSV	AACC	0.063	0.0001	0.064	0.001	0.36
F	DSV	CC	0.063	0.020	0.095	0.032	0.21
F	DSV	SS	0.076	0.0049	0.082	0.0060	0.29
B	DSV	CHOL	0.024	0.025	0.045	0.021	0.68
B	DSV	NON-CHOL	0.024	0.013	0.029	0.005	0.78
B	DSV	SAA	0.068	0.0005	0.068	0	0.27
B	DSV	WMH ALL	0.050	0.022	0.079	0.0290	0.28
B	DSV	AACC	0.050	0.0026	0.059	0.0090	0.39
B	DSV	CC	0.050	0.064	0.13	0.080	0.12
B	DSV	SS	0.065	0.0039	0.071	0.0060	0.35
NT	STV	CHOL	0.35	0.0055	0.36	0.010	0.024 *
NT	STV	NON-CHOL	0.35	0.33	0.56	0.21	0.0009 *
NT	STV	SAA	0.41	0.0091	0.42	0.010	<0.0001 *
NT	STV	WMH ALL	0.38	0.019	0.42	0.040	0.0002 *
NT	STV	AACC	0.38	0.001	0.40	0.020	0.0004 *
NT	STV	CC	0.38	0.0088	0.41	0.030	0.0003 *
NT	STV	SS	0.35	0.0028	0.36	0.010	0.0016 *
F	STV	CHOL	0.20	0.029	0.23	0.030	0.10
F	STV	NON-CHOL	0.20	0.0022	0.202	0.0020	0.15
F	STV	SAA	0.26	0.077	0.30	0.040	0.0015 *
F	STV	WMH ALL	0.20	0.0021	0.21	0.010	0.028 *
F	STV	AACC	0.20	0.0001	0.21	0.010	0.028 *

Table 19 (continued)

F	STV	CC	0.20	0.0027	0.21	0.010	0.025 *
F	STV	SS	0.21	0.11	0.32	0.11	0.0037 *
B	STV	CHOL	0.26	0.037	0.28	0.020	0.061
B	STV	NON-CHOL	0.26	0.12	0.31	0.050	0.045 *
B	STV	SAA	0.32	0.0002	0.33	0.010	0.0007 *
B	STV	WMH ALL	0.32	0.016	0.36	0.040	0.001 *
B	STV	AACC	0.32	0	0.34	0.020	0.0018 *
B	STV	CC	0.32	0.033	0.38	0.060	0.0005 *
B	STV	SS	0.33	0.0005	0.33	0	0.0027 *
NT	SEV	CHOL	0.21	0.0009	0.21	0	0.14
NT	SEV	NON-CHOL	0.21	0.24	0.37	0.16	0.020 *
NT	SEV	SAA	0.25	0.006	0.25	0	0.0053 *
NT	SEV	WMH ALL	0.23	0.0075	0.24	0.010	0.013 *
NT	SEV	AACC	0.23	0.001	0.23	0	0.018 *
NT	SEV	CC	0.23	0.0052	0.25	0.020	0.013 *
NT	SEV	SS	0.21	0.015	0.23	0.020	0.023 *
F	SEV	CHOL	0.25	0.024	0.27	0.020	0.077
F	SEV	NON-CHOL	0.25	0.011	0.25	0	0.11
F	SEV	SAA	0.20	0.0303	0.21	0.010	0.0142 *
F	SEV	WMH ALL	0.18	0.0022	0.18	0	0.047 *
F	SEV	AACC	0.18	0.0027	0.19	0.010	0.046 *
F	SEV	CC	0.18	0.0041	0.18	0	0.047 *
F	SEV	SS	0.21	0.046	0.26	0.050	0.015 *
B	SEV	CHOL	0.19	0.098	0.27	0.080	0.080
B	SEV	NON-CHOL	0.19	0.34	0.43	0.24	0.012 *
B	SEV	SAA	0.21	0.012	0.24	0.03	0.0077 *
B	SEV	WMH ALL	0.25	0.0097	0.28	0.03	0.0075 *
B	SEV	AACC	0.25	0	0.27	0.02	0.0099 *
B	SEV	CC	0.25	0.0049	0.27	0.02	0.0088 *
B	SEV	SS	0.29	0.032	0.33	0.04	0.0036 *

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