WHITE MATTER HYPERINTENSITIES AND LOWER EXTREMITY PHYSICAL FUNCTION BEFORE AND AFTER AN AEROBIC EXERCISE INTERVENTION IN HEALTHY OLDER ADULTS

BY

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DISSERTATION

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ABSTRACT

Background: Age-related declines take many forms including white matter deterioration, cognitive impairments, and mobility limitations, all of which can have practical implications, such as falling and making risky pedestrian decisions. Modifiable lifestyle interventions, like physical activity, provide ways to mitigate or ameliorate the range of age-related declines. This dissertation examined the relationships between lower extremity physical function and a representative measure of age-related cerebral small vessel disease, white matter hyperintensity (WMH) volume in the brain, before and after an aerobic exercise intervention in a sample of relatively young and healthy older adults. Analyses also examined the role of WMH volume, physical function, and cognition on virtual reality street crossing risk assessment.

Methods: Data were analyzed from 177 older adults (M age = 65) who completed the Fit and Active Senior Trial (FAST), a six-month physical activity intervention including three groups: stretching, strengthening, and stability (SSS); dance (Dance); aerobic walking (Walk).

Results: The baseline relationship between greater WMH volume and worse lower extremity physical function was weak in this sample and, unsurprisingly, WMH volume did not change over the six-month intervention. Regardless of intervention group, greater standardized improvement in lower extremity physical function was significantly predicted by lower baseline WMH volume, greater baseline gait self-efficacy, and better baseline fitness, uniquely and in interaction. In a separate model, greater improvements in lower extremity physical function were observed in adults assigned to the Dance condition who had greater improvement in gait self-efficacy and/or lower initial WMH volume.

Conclusions: The results reported here suggest that in sedentary older adults, the transition to physically active can benefit lower extremity physical function regardless of the type of

activity. However, these gains seem to be greatest over the six-month period in individuals who at baseline have lower WMH volume, better gait self-efficacy, and better fitness.

To my family (by blood and choice) for their unconditional love and support.

“Ph’nglui mglw’nafh Cthulhu R’lyeh wgah’nagl fhtagn.”

(”In his house at R’lyeh, dead Cthulhu waits dreaming.”)

- H.P. Lovecraft, The Call of Cthulu

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CHAPTER 1

AGE-RELATED CHANGES

Over the last 40 years, a growing portion of the total population has consisted of adults over 60 years old. This is a result of declining birth rates and increasing life expectancies (National Institute on Aging, 2011). Along with age-related deteriorating cognitive abilities, structural brain changes, and declining mobility comes the inability to live independently for many older adults, especially the oldest old (National Institute on Aging, 2011). In recent years, researchers have studied potential lifestyle interventions in hopes of improving the quality of life of our oldest citizens and reducing the inevitable financial and logistical burdens an aging population places on society (Beard & Bloom, 2015; Mendelson & Schwartz, 1993).

This chapter discusses age-related structural brain changes specifically focusing on the influence of cerebral small vessel disease (SVD). Portions of this chapter focus on white matter hyperintensities (WMHs), namely how they are measured and how they relate to cognition in older adults.

1.1 Structural brain changes and cerebral small vessel disease

Healthy aging causes many changes to brain structure. However, there is inter-individual heterogeneity in the type and extent of brain deterioration in healthy aging populations (Wardlaw, Hernández, & Muñoz-Maniega, 2015). Understanding the implications and neurobiology of healthy brain aging is further complicated by damage to the blood vessels in the brain known as SVD (Gouw et al., 2010; Wardlaw et al., 2013).

A number of vascular risk factors contribute to the development of SVD, such as diabetes and smoking (Söderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003; Wardlaw et al., 2015). Yet, these risk factors are not consistently identified. For example, a number of studies identified high blood pressure as an indicator of SVD (DeCarli et al., 1995; Firbank et al., 2007), while others reported no relationship (Whitman, Tang, Lin, & Baloh, 2001). These inconsistencies may indicate that different measurement techniques are needed to uncover underlying pathologies of SVD.

SVD encompasses several structural brain abnormalities including lacunes, infarcts, microbleeds, perivascular spaces, and WMHs. All of these features can be identified on computed tomography (CT) and magnetic resonance (MR) images. See Figure 1 below for examples of each of these abnormalities.

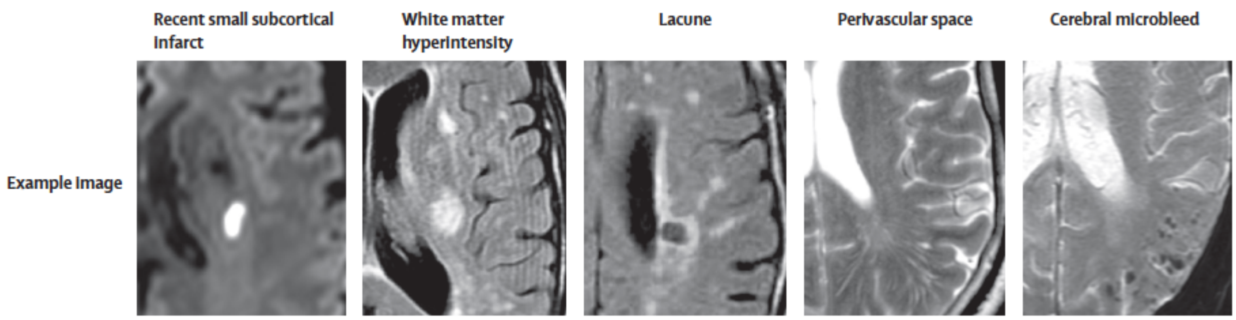

Figure 1: Structural abnormalities associated with small vessel disease. Image taken from Wardlaw et al., 2013.

These manifestations of SVD can be difficult to distinguish on CT or MR scans. As a result, some researchers compile these measures into a global measure of SVD presence (Staals et al., 2015). In other cases, trained researchers or neuroradiologists manually evaluate individual subtypes of SVD burden (Ishikawa, Meguro, Ishii, Tanaka, & Yamaguchi, 2012).

1.2 White matter hyperintensities

WMHs have been singled out as a representative measure of SVD and, more broadly, age-related structural brain deterioration. The pathogenesis of WMHs includes ischemia, changes in the blood-brain barrier permeability, edema, and loss of autoregulation of cerebral blood flow (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Pantoni, 2002; Gregory, Gill, & Petrella, 2013). These biological changes are not necessarily unique to SVD but contribute to the progression of WMHs in aging.

These areas of increased signal on T2-weighted MR scans are commonly encountered in aging populations, yet, identifying and quantifying WMHs has proven to be difficult. WMH measurement and evaluation has fallen prey to many of the same complications as general SVD assessment.

1.3 Quantifying WMHs

Two broad methodological approaches for evaluating WMHs are used by researchers: visual rating scales and segmentation of affected areas. Two categorical visual rating scales commonly used are the Fazekas and Scheltens scales. The Fazekas scale consists of four levels of WMH severity, with zero indicating no WMHs and three indicating lesions or confluent areas of hyperintensity 20 mm in diameter (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). The Sheltens scale uses a more localized assessment of WMH severity and requires raters to evaluate periventricular regions and subcortical regions separately (Prins & Scheltens, 2015).

Methodologies used for segmenting WMHs are more varied. Researchers may collect fluid-attenuated recovery (FLAIR; Maillard et al., 2013; Callisaya et al., 2013), non-FLAIR T2-weighted (Burzynska et al., 2014), or T1-weighted (de Laat et al., 2010) images from which to assess WMH burden, or the quantity of affected areas. FLAIR images permit the recruitment of an automatic algorithm for WMH segmentation (Firbank et al., 2007). While a manual check of the resulting image masks is necessary, this is often considered to be the gold standard (Caligiuri et al., 2015). WMH evaluation is also possible on non-FLAIR images or on FLAIR images without using an automated segmentation technique (Burzynska et al., 2014; Callisaya et al., 2013). These cases require a trained rater to manually classify areas as WMHs. (Maillard et al., 2013).

These identifications are guided by the standard classification of two types and locations of WMHs. Periventricular WMHs are described as caps on the frontal or occipital horns, which can extend transversely along the lateral ventricle walls (Prins & Scheltens, 2015). They vary in size but can extend from the ventricles diffusely. By contrast, deep matter WMHs are punctuate foci in subcortical white matter. While many researchers distinguish these two types of WMHs believing they may have different risk factors or clinical implications (Wardlaw et al., 2013), others researchers collapse the subtypes and use a total WMH volume measure (Arvanitakis et al., 2016; Birdsill et al., 2014; Gunning-Dixon & Raz, 2000).

Generally, WMH burden increases with age (Silbert, Nelson, Howieson, Moore, & Kaye, 2008; Moscufo et al., 2012; DeCarli et al., 2005) and individuals with greater WMH volume initially tend to have an increased rate of WMH accumulation over time (Whitman et al., 2001; Silbert et al., 2008; Maillard et al., 2013; Wen, Sachdev, Li, Chen, & Anstey, 2009). Although there are many other alterations to brain structure that occur with healthy aging, greater WMHs are one such measure that is frequently linked with accelerated cognitive and mobility declines in older adults.

1.4 White matter hyperintensities and cognition

Deficits across most cognitive domains are consistently demonstrated throughout aging research. For example, Park and colleagues (2002) reported that after age 20, adults exhibit steady declines in measures of processing speed and fluid intelligence, as well as short-term, long-term, and working memory performance. Semantic knowledge was the only domain in which adults improved across the lifespan, until a plateau in later life (Park et al., 2002). Age-related cognitive deficits are particularly noticeable when individuals must switch between two tasks (Kray & Lindenberger, 2000; Kramer, Larish, & Strayer, 1995) or conducting two tasks simultaneously (Vaportzis, Georgiou-Karistianis, & Stout, 2013).

These cognitive declines are associated with many of the structural changes occurring in the aging brain, one of which is the development of WMHs. Processing speed and executive functions negatively relate to WMHs, such that greater WMH burden indicates impaired performance in these domains, often regardless of WMH location (Gunning-Dixon & Raz, 2000; Arvanitakis et al., 2016; Birdsill et al., 2014; Oosterman et al., 2008; Parks et al., 2011; Söderlund et al., 2003; Ylikoski et al., 1993; Debette & Markus, 2010; Dufouil, Alperovitch, & Tzourio, 2003; Papp et al., 2014; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009; Murray et al., 2010; Hernández et al., 2013). These findings are not affected by methodological differences in WMH measurement. WMH volume is also associated with an increased risk of clinical outcomes including mild cognitive impairment and Alzheimers Disease (Boyle et al., 2016; Prins & Scheltens, 2015; Wallin & Fladby, 2010).

However, not all findings are as consistent. For example, some studies convey a negative relationship between episodic memory and WMHs (He et al., 2012), while others report no significant relationship (Arvanitakis et al., 2016) or no relationship independent of other cognitive measures (Parks et al., 2011). Episodic memory is not the only cognitive domain with inconsistencies. In some studies, WMHs are reported to have a weak or no significant relationship with cognitive measures across the board (Borghesani et al., 2013; Staals et al., 2015; Mueller et al., 2010). Some of these inconsistent findings can be explained by variance in the pathological severity of WMHs (Wardlaw et al., 2015).

WMHs are associated with SVD and deteriorating brain health in older adults. However, using WMHs as a metric presents several potential limitations, including assessment inconsistency and low variability in healthy samples. Despite these shortcomings, WMHs reliably show a relationship with processing speed and executive functions in healthy older adults. The following chapter discusses practical implications of age-related deteriorations to brain health and executive functions, including applications to older adult physical function, risky behaviors, and independent living.

CHAPTER 2

PHYSICAL FUNCTION CHANGES IN AGING ADULTS

Physical function and mobility impairments have important implications for the independence of aging populations (e.g., von Bonsdorff, Rantanen, Laukkanen, Suutama, & Heikkinen, 2006). This chapter discusses mobility, specifically lower extremity physical function, and its connection to age-related shifts in cognition and WMHs. The final portion of the chapter discusses real-world implications of mobility declines, specifically increased risk of falling and pedestrian risk assessment.

2.1 Mobility and cognition

Cognitive abilities are often studied in relation to or as potential predictors of deteriorating mobility. In aging research, mobility can include a wide range of physiological and behavioral measures. Comprehensive mobility assessments, such as the physiological profile assessment (Lord, Menz, & Tiedemann, 2003) and the Tinnetti scales (Tinetti, Williams, & Mayewski, 1986), include many physiological measures to form a complete picture. However, individual measures of gait or lower extremity physical function are frequently used for a more focused assessment. Gait measures include: gait variability, stability, speed, and cadence. Lower extremity physical function measures can include an individual's ability to stand and sit, climb and descend a flight of stairs, and walk around a cone starting from a seated position.

Researchers studying the relationship between mobility and cognitive or brain aging use any one or combination of these mobility assessments. Better physical function, measured through broad assessments, has been related to better executive functioning, specifically set shifting, working memory, and inhibition (T. Y. Liu-Ambrose, Ashe, Graf, Beattie, & Khan, 2008). Similar relationships between executive functions, including set shifting, inhibition, and attentional flexibility, as well as processing speed, have also been reported using lower extremity physical function measures (Gothe et al., 2014; Williamson et al., 2009). Furthermore, a recent review by Amboni, Barone, and Hausdorff (2013) included significant associations between individual gait measures (specifically variability and speed) and executive function performance. This series of findings demonstrates a consistent and replicable relationship between better mobility, via a variety of assessments, and a range of cognitive tasks.

This body of literature seems to suggest a feedback loop between cognitive and physical impairments both of which contribute to older adults' inability to perform everyday tasks. For example one study concluded that, although cognitive decline begins prior to the physical impairment in older adults, the rate of cognitive decline increases 30% after the onset of physical limitations (Rajan, Hebert, Scherr, de Leon, & Evans, 2015). They posited that deterioration in old age occurs stepwise, so early physical limitations can provide an early indication for the extent of future cognitive decline.

2.2 Physical function and WMHs

Beyond cognitive performance, brain health also relates to declining mobility in older populations. This link likely results from age-related disruption of tracts in the periventricular and subcortical regions known for linking motor function and executive control (Srikanth et al., 2010; Moscufo et al., 2011; Koo et al., 2012). WMHs contribute to this disruption and, as such, also relate to age-related physical function impairments.

In a number of cases, greater WMH burden predicted greater balance dysfunction and detrimental changes in gait performance (Silbert et al., 2008; Baloh, Ying, & Jacobson, 2003; Whitman et al., 2001; Camicioli, Moore, Sexton, Howieson, & Kaye, 1999; Baezner et al., 2008; Srikanth et al., 2008, 2010; Rosano, Brach, Longstreth Jr, & Newman, 2006; de Laat et al., 2011, 2010). Furthermore, a greater rate of WMH progression over several years predicted a greater detriment to mobility and physical function measures, such as gait speed, 8-foot-up-and-go, and chair stands (Callisaya et al., 2013; Moscufo et al., 2012; Rosano et al., 2010). Despite these numerous findings, cases remain where WMHs do not relate to measures of mobility (Rosano, Aizenstein, Studenski, & Newman, 2007) or do so weakly (Rosano, Brach, Studenski, Longstreth Jr, & Newman, 2007).

2.3 Risk of falling

Maintaining physical function in aging populations is a critical task. Age-related physical function impairments result in an increased risk of falling and the inability of older adults to live independently (Mendelson & Schwartz, 1993; Kramer, Erickson, & Colcombe, 2006; Whitman et al., 2001; von Bonsdorff et al., 2006).

There are a range of risk factors that contribute to falls risk. Boelens, Hekman, and Verkerke (2013) divided risk factors for falling into intrinsic, extrinsic, and behavioral categories. Intrinsic factors are related to internal biological factors. For example, greater risk of falling is inconsistently associated with sex (Blake et al., 1988; Grundstrom, Guse, & Layde, 2012), age, obesity, osteoporosis, arthritis, sleep disturbances, and cognitive ability (Eshkoor, Hamid, Nudin, & Mun, 2013; Boelens et al., 2013). External factors contributing to falls risk are related to an individuals living space. Few have been examined, though one study reported that risk of falling is greater in the afternoon (Boelens et al., 2013). The final category of risk factors is behavioral, including actions taken by the individual. These factors have been much more extensively studied. Behavioral factors that are linked to greater risk of falling include more risk-taking behaviors, heightened fear of falling, and greater physical inactivity (Mitchell, Lord, Harvey, & Close, 2014; Boelens et al., 2013; McAuley, Szabo, Gothe, & Olson, 2011).

2.4 Real world concerns, cognition, and WMHs

Several of the same cognitive measures that relate to mobility impairments extend to predict greater risk of falling in older populations (Bridenbaugh & Kressig, 2015; Hsu, Nagamatsu, Davis, & Liu-Ambrose, 2012). For instance, when followed for a five-year study, older adults with lower executive function performance were more likely to fall (Mirelman et al., 2012). The researchers further reported that older adults with lower baseline executive function were more likely to fall multiple times over the study period. Additionally, age-related structural brain changes, including greater WMH burden, also correlated with a greater risk of falling in older adults (Morley, 2015).

In everyday tasks, functional impairments translate into less independence and greater risk of injury or accident, including the 19% of fatal pedestrian accidents accounted for by older adults (National Highways Traffic Safety Administration, 2013). To better understand how age-related differences in cognition contribute to street crossing behavior, Neider and colleagues (2011) used an immersive virtual reality street crossing task to study the effects of multitasking (i.e., listening to music; talking on a hands-free phone) on street crossing performance. Older adults showed greater dual-task costs to crossing success, as well as a larger increase in the time to decide to initiate a crossing, suggesting that older adults had greater difficulty making decisions when engaged in a concurrent naturalistic phone conversation (Neider et al., 2011). Furthermore, expanding on previous literature examining the relationship between mobility and falls and cognitive performance, Nagamatsu and colleagues (2011) reported that performance on the same virtual street crossing task was negatively related to falls risk in seniors. Results from this real-world paradigm parallel the findings from standard laboratory tasks showing that age-related cognitive impairments, especially in executive functioning, are related to poorer and less safe outcomes (Butler, Lord, & Fitzpatrick, 2016; Geraghty, Holland, & Rochelle, 2016; Tournier, Dommes, & Cavallo, 2016).

Mobility and lower extremity physical function show strong connections with executive functions and WMHs. The ability to live independently in older age suffers with declining physical, impaired cognition, and deteriorating brain health. Thus, it is particularly important to understand what adaptable behaviors, such as physical activity, can be modified to improve physical function and reduce subsequent dangers preventing older adults from living independently.

CHAPTER 3

PHYSICAL ACTIVITY IN AGING

Physical activity has been demonstrated to have beneficial cognitive and brain effects in aging populations. This chapter addresses some ways in which physical activity benefits cognition. There is also a brief discussion of the biological pathways through which physical activity works and the established relationship between physical activity and WMHs. This chapter concludes with an overview the contributions this dissertation will make to the extant literature.

3.1 Physical activity and cognition

Physical activity is consistently identified as a mitigating factor in age-related cognitive declines (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). Strong links are regularly reported between physical activity and a range of cognitive functions, such as working memory, processing speed, and episodic memory (Erickson et al., 2011; Lautenschlager et al., 2008; Colcombe & Kramer, 2003; Bherer, Erickson, & Liu-Ambrose, 2013; Institute of Medicine of the National Academies, 2015). These findings suggest that physical activity has a role in enhancing cognition and buffer against age-related cognitive decline.

Physical activity interventions are often engaged to lessen age-related declines in both cognitive ability and physical function. These interventions often include resistance (strength) training or aerobic activities (e.g. running, jogging, cycling, walking, swimming, etc.). The effectiveness of these interventions is determined by many factors including the duration, intensity, or type of exercise (Colcombe & Kramer, 2003; Barha, Galea, Nagamatsu, Erickson, & Liu-Ambrose, 2016; Kramer & Erickson, 2007; DiPietro, 2001). Some studies further suggest aerobic fitness is key to deriving cognitive benefits (Barnes, Yaffe, Satariano, & Tager, 2003; Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008), while others conclude that any type of physical activity can be valuable and should be encouraged in older adults (DiPietro, 2001).

3.2 Biological pathways of physical activity

Resistance and aerobic interventions affect the body and brain via different biological mechanisms. Despite these different pathways, both types of exercise exert a benefit on cardiovascular risk (Gregory et al., 2013; Cornelissen & Fagard, 2005; Strasser, Siebert, & Schobersberger, 2010; Xu et al., 2014; Uemura et al., 2012).

There are many biological factors directly affected by physical activity. One such example is angiogenesis (Bherer et al., 2013; Voss, Vivar, Kramer, & van Praag, 2013). Physical activity stimulates this formation of new blood vessels, which generally occurs during childhood development. The increase in microvascular density may protect against brain deterioration, including grey matter atrophy and WMH development, as well as cognitive impairments. Exercise also affects neurogenesis in specific regions of the brain, particularly the hippocampus. These biological mechanisms likely contribute to the widespread cognitive benefits and enhanced brain health, which result from an increase in physical activity.

On a molecular level, a number of neurochemicals, such as brain-derived neurotrophic factor, insulin-like growth factor 1, and serotonin, play critical roles in neuroplasticity (Erickson et al., 2011; Firbank et al., 2007; Bherer et al., 2013; Ahlskog, Geda, Graff-Radford, & Petersen, 2011; Kramer et al., 2006). Other health factors such as stress, hypertension, and diabetes also can influence the efficacy of physical activity in benefitting the aging brain (Dishman et al., 2006; Bherer et al., 2013). A number of other potential factors may help to explain the relationship between physical activity and its benefits to cognitive and brain health.

Since most studies involving humans tend to lack the ability or resources to examine these fine-grained biological mechanisms, they focus on more accessible metrics. By using brain-imaging techniques such as MRI, researchers study structural and functional changes in the brain that result from physical activity-induced alterations to biological mechanisms. Specifically, several age-related changes to brain structure and function altered by physical activity and can be observed on MR images. Researchers have reported that greater physical activity in older adults can slow grey and white matter atrophy, as well as increase regional task-based activation and functional connectivity (Voss et al., 2010; Bherer et al., 2013; Weinstein et al., 2012; Colcombe et al., 2004, 2006). Aerobic exercise interventions have also been linked to increased volume in the hippocampus (Erickson et al., 2011). Moreover, Tseng and colleagues (2013) reported better maintenance of WM integrity in individuals who were life-long athletes.

3.3 Physical activity and WMHs

WMH burden is a specific aspect of WM deterioration that benefits from a physically active lifestyle (Gow et al., 2012) and increased fitness (Tseng et al., 2013). Burzynska and colleagues (2014) reported that participants who engaged in more moderate to vigorous physical activity had better white matter integrity, measured through fewer WMHs. As previously noted, Voss and colleagues (2013) posited a possible explanation for this relationship- the increase in microvascular density resulting from physical activity is neuroprotective and can result in slower progression of WMHs.

In a recent review, Torres and colleagues (2015) examined studies of physical activity and WMHs. The authors concluded that greater physical activity generally related to less WMH burden. However, these results were not consistent across all studies evaluated. The negative link between physical activity and WMH burden was more likely to be significant if the study was conducted outside of the US, included longitudinal or physical activity data from across the lifespan, used objective physical activity measures, manually or semi-automatically segmented WMHs, and/or controlled for additional risk factors (Torres et al., 2015). Another display of inconsistency was shown in a sample largely consisting of older adults with Alzheimers disease or mild cognitive impairment. In this sample, the rate of WMH progression was unrelated to physical activity (Podewils et al., 2007). These demonstrated inconsistencies suggest that the complex relationship between WMHs and physical activity might be weaker in less healthy older adults.

3.4 Contributions

Understanding the role of modifiable behaviors, such as physical activity, in mitigating negative age-related changes could play a large role in ensuring adult independence into old age. It is also important to understand the potential influence of the pre-existing state of WM deterioration, which may impact the effectiveness of lifestyle interventions.

While several studies have examined the individual links between physical activity and WMHs, WMHs and mobility, and physical activity and mobility, Bolandzadeh and colleagues (2015) took a comprehensive look at all three elements together. They conducted a yearlong resistance training intervention with older female adults. The researchers reported that the group who underwent resistance training twice weekly had lower WMH volume compared with the stretching control group at the end of intervention. The results also showed a relationship between slower rate of WMH progression and better maintenance of gait speed for the twice-weekly resistance training group, and not the once-weekly resistance training condition or the stretching control. This dissertation expands on their research and others like it by focusing on older adults who underwent an aerobic physical activity intervention and studying the influence of pre-existing WMH volume on lower extremity physical function improvements.

CHAPTER 4

THE FIT AND ACTIVE SENIORS TRIAL

The Fit and Active Seniors Trial (FAST) was a six-month physical activity intervention conducted at the University of Illinois at Urbana-Champaign. The longitudinal intervention included neuropsychological testing, physical function and fitness testing, as well as a series of magnetic resonance imaging (MRI) scans prior to commencing the intervention sessions. Participants attended three, one-hour sessions per week for six months. Following the final intervention session, participants returned for second neuropsychological, physical function, fitness, and MRI sessions.

4.1 Participants

Potential participants were recruited from advertisements and fliers in the Urbana-Champaign community. Participation criteria required individuals to be between the ages of 60-85 years, sedentary, right-handed, have no diagnosed brain injuries or neuropsychological disorders, and have no metal implants that would prevent MRI from being conducted. Those individuals satisfying the initial criteria were screened for health and cognitive deficits by a structured phone interview including the geriatric depression scale (GDS-5), modified telephone interview for cognitive status (TICS-M), and the mini-mental state examination (MMSE). Participants scoring above or equal to two on the GDS-5, below 21 on the TICS-M, and below a 23 out of 30 on the MMSE were disqualified from participating in the study.

The study sample consisted of 247 older adults between the ages of 60-79 (M = 65, 169 female). Due to study attrition, missing data, outlying data exclusion, and MR image artifacts, there were 177 participants with WMH, physical function, gait self-efficacy, and VO_2 max data at baseline, and 167 with longitudinal data for those measures (see Figure 2). Finally, the last set of analyses included the virtual reality street crossing task and a general cognitive performance covariate. Because 68 participants were missing either street crossing or cognitive testing, this analysis included 116 participants.

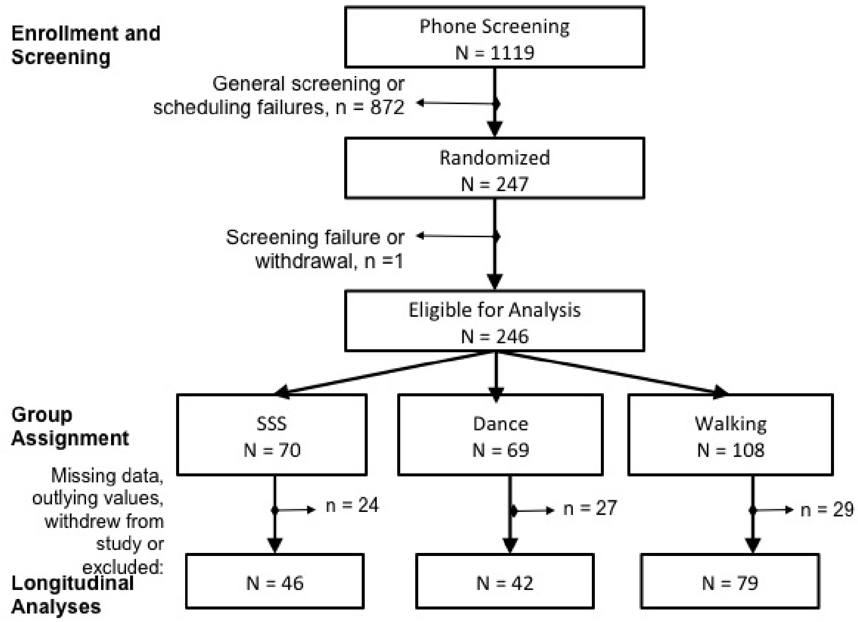

Figure 2: FAST study enrollment.

4.2 Intervention Details

Eligible participants were assigned to one of three conditions: stretching, strengthening, and stability (SSS); dance (Dance); or aerobic walking (Walk). All intervention sessions were supervised by trained exercise leaders and began and ended with stretching.

The SSS group was guided through a series of 10-12 exercises focusing on flexibility, strength, and balance during each session. Participants were able to do each exercise in one of three varying difficulty levels. Over the course of the intervention, new and more challenging exercises were introduced.

The Dance condition consisted of social dancing sessions including mostly American and English folk dancing. The Walk condition included participants walking at 50-60% of their maximal heart rate, as assessed by a maximal graded exercise test, increasing from 20-40 minutes in duration. Following week seven of the intervention, participants walked at 60-75% of the maximal heart rate for 40 minutes.

4.3 MRI Methods

T2-weighted images were acquired on a 3T Siemens Trio Stim system. T2-weighted images consisted of 35 4-mm-thick slices (in-plane resolution of 0.86 mm x 0.86 mm, 256 x 256 matrix, TR/TE = 2400/63 ms, FA = 120). WMH volume was estimated using a semi-automated procedure (Burzynska, et al., 2010) based on FMRIB's Automated Segmentation Tool (FAST in FSL v.5.0.1). The procedure included removal of the skull and non-brain tissue using the Brain Extraction Tool (Smith et al., 2002) followed by segmentation of the image into grey matter, white matter, and cerebrospinal fluid. Finally, WMH regions were manually masked within the white matter segmentation by two independent trained raters (Inter-rater reliability: ICC $> .9$). As with previous studies, WMH volume was log transformed to normalize the distribution. Other MRI measures were collected from intervention participants but were not discussed here.

4.4 Lower-Extremity Physical Function

Five measures were included to assess aspects of lower body strength, balance, and agility: stair ascent and descent, chair stands, 8-foot up and go, and right leg stand (Podsiadlo & Richardson, 1991; Rikli & Jones, 2001).

4.4.1 Stair climb test

Participants walked up and down a flight of 15 stairs while timed by two scorers. Times were averaged to calculate scores for the ascent and decent portions separately. Shorter time to complete the trials indicated better physical function.

4.4.2 Chair stand test

Participants started seated in a chair with their arms crossed against their chests, rose to a full stand, and returned to a fully seated position in the chair. Participants were instructed to do this as many times as possible within a timed 30-second interval without any assistance. Completing a greater number of chair stands indicated better physical function.

4.4.3 Timed 8-foot Up-and-Go

Participants started seated in a chair, stood and walked eight feet around a cone, and returned to a seated position. Two trials were completed and times were averaged. Shorter time to complete the trial indicated better physical function.

4.4.4 Leg stand

Participants stood unassisted on one leg as long as possible. Longer time standing on one leg indicated better balance. All participants were right handed, thus right, or dominant, leg stand time was used for statistical analyses.

4.5 Gait Self-Efficacy

The Gait Efficacy Scale (GES; McAuley, Mihalko, & Rosengren, 1997) was used to assess individuals' beliefs in their ability to walk despite obstacles, including stairs or objects in their path. Each of the six items were scores from 0-100% and then averaged for an overall score.

4.6 Cardiorespiratory Fitness

Cardiorespiratory fitness (VO_2 max) was assessed with a graded maximal exercise test on a motor-driven treadmill. Briefly, oxygen consumption (VO_2) was calculated from expired air sampled at 30 s intervals until peak VO_2 max was reached or the test was terminated due to exhaustion and/or physical limitation.

4.7 Cognitive Assessments

Seventeen cognitive assessments were obtained measuring working memory, executive functions (specifically cognitive flexibility, fluid intelligence, and spatial reasoning), processing speed, episodic memory, and vocabulary (see Appendix A for a detailed list of tasks). Computer-based tasks were designed in E-prime version 1.1 (Psychology Software Tools, Pittsburgh, PA) and administered on computers with 17 cathode ray tube (CRT) monitors.

4.8 Street Crossing Paradigm

This virtual street crossing environment was developed in the virtual reality Cave Automatic Visual Environment (CAVE) at the University of Illinois at Urbana-Champaign (http://www.isl.uiuc.edu/Labs/CAVE/CAVE.html; Neider, McCarley, Crowell, Kaczmarski, & Kramer, 2010). Briefly, participants walked on a Woodway "Curve" manual treadmill that was linked with a virtual environment. Images of this environment were projected onto three screens measuring 303 cm wide by 273 cm high. On each trial, the participant started from an alleyway before a busy street, approached the roadway and crossed when deemed safe. The cars were all travelling at 33 mph, while the inter-vehicle distance varied between trials: either 75 or 90 m. Head position and orientation was measured with an Ascension Flock of Birds 6 DOF electromagnetic tracker. Head movements were counted when the participant moved at least 10° in one direction followed by the same amount in the other direction. CrystalEyes liquid crystal shuttle goggles created the illusion of depth in the virtual environment.

Dual-task load was manipulated within participants. In the single-task no distraction condition, participants crossing the street without any distraction. During the dual-task phone condition, participants were engaged in a hand-free phone conversation with the experimenter while crossing the street.

The trial timed out if the subject took longer than 90 s to make it across the street successfully. The few trials that were not completed due to timing out were excluded from all analyses. Participants completed two blocks of ten trials in each condition, for a total of 40 trials; the order of these blocks was randomized across participants. Eight practice trials were administered prior to the start of the experiment to allow participants to gain familiarity with the manual treadmill as well as the task.

Risk assessment during the task was measured as the time until the virtual car would collide with the participant's position, called time to contact (TTC). TTC was measured at two time points during each trial: as the participant entered the street (immediate) and as the participant was exiting the street (delay). Lower TTC values indicated a riskier choice.

4.9 Statistical Analyses

Statistical analyses were conducted in IBM SPSS Statistics (Version 22) for Mac (Chicago, IL). Values outside of 3 SD from the mean were excluded from analyses and supplemental analyses were held to Bonferroni correction for multiple comparisons.

CHAPTER 5

ANALYSES AND HYPOTHESES

5.1 Analysis 1: Baseline relationship between WMHs and physical function

Pre-intervention cross-sectional differences in WMH predicting lower extremity physical function– a composite of multiple measures– were tested in a stepwise regression framework. The first level of this analysis was designed to account for demographic variables and therefore included age, sex, and cardiovascular disease history. The second level assessed the relationship between WMH volume and physical function; it included WMH volume. Given the existing literature, I expected greater baseline WMH volume to be associated with worse physical function scores. This analysis served to reproduce previous reports in a novel sample of relatively young older adults. A third level including gait self-efficacy and VO_2 max was included to assess the impact of these variables in a competing model with WMH volume and demographic variables. This level proffered two additional measures I expected to positively relate to lower extremity physical function.

The sample of 177 participants included in bivariate analyses was sufficient to detect a moderate effect size to significance (critical F=3.89, f2 = .07; = 0.05, = 0.95; G*Power). The same sample size was also able to detect a similar effect size when accounting for three additional covariates: age, sex, and cardiovascular disease history (critical F= 2.42, f2 = .11; = 0.05, = 0.95; G*Power).

5.2 Analysis 2: Longitudinal assessment of change in WMH and physical function, and possible intervention group differences

Initially, intervention groups were tested for differences in age, sex, and cardiovascular disease history. Longitudinal change in WMH volume was assessed over the six-month aerobic physical activity intervention using a two-level (Pre- vs. Post-intervention) repeated measures general linear model (GLM). Because WMHs are a gross indicator of WM deterioration and most studies examining their progression extend beyond a year (Moscufo, et al., 2012; Callisaya, et al., 2013; Bolandzadeh et al., 2015), I did not expect WMH volume to significantly change between pre- and post-intervention imaging.

To evaluate predictors of physical function change, a standardized change score was calculated– the standardized residual values from regressing the pre physical function factor values on post. This change score was used as the dependent variable in a univariate GLM including intervention group, baseline WMH volume, baseline gait self-efficacy, and baseline VO_2 max as predictors. All two- and three-way interactions were eliminated from the model if not significant.

I expected the greatest physical function improvements in the aerobic Walk group. The older adults in this study were recruited specifically because they did not regularly engage in physical activity prior to recruitment and were considered sedentary. Any level of increased physical activity was expected to benefit lower body strength in this sample. However, the greatest gains were expected from the aerobic Walk condition (Paterson & Warburton, 2010).

I also expected a relationship between greater improvements in physical function and greater baseline WMH volume, lower gait self-efficacy, and lower VO_2 max. Age-related declines in vascular health are at the root of both increasing WMH burden as well as deteriorating physical function, and I anticipated that an intervention aimed at improving aerobic health would be able to benefit both of these. Therefore, I hypothesized that individuals who were already in a state of white matter decline were likely to show greater benefits to physical function from the aerobic intervention.

A second longitudinal model of physical function change included standardized change in gait self-efficacy and VO_2 max, replacing their baseline values in the previous model. Again, all two- and three-way interactions were eliminated from the model if not significant. As with the previous analysis I hypothesized that, in addition to larger physical function improvements in the Walk condition, individuals with greater improvements in gait self-efficacy and VO_2 max would also show greater improvements in physical function.

5.3 Analysis 3: Cognitive applications of WMHs and physical function- Virtual Street Crossing

While the first two sets of analyses examined predictors of lower extremity physical function and change over the physical activity intervention, this final analysis explored a real-world application of lower extremity physical function. Risk assessment at entering and exiting the street were assessed in a two-way (Lane: Entry vs. Exit) repeated measures GLM. Baseline WMH volume, baseline physical function, age, sex, and cardiovascular disease history were included in the model as predictors. Crossing duration, the length of time taken to cross the street, also was included in the model to account for motor ability. All two- and three-way interactions were eliminated from the model if not significant.

Successful trials were isolated to examine the individual differences in immediate and delayed risk assessment, particularly as a function of baseline WMH. Although complete failures in risk assessment are an indicator of unsuccessful trials, it would have been difficult to assess the meaningfulness of individual differences within a context of categorical failure. Examining variability in risk assessment during successful trials provided a better model for the real-world scenario of unsafe but nonetheless successful street crossing. I expected adults with worse physical function and greater WMH volume to make riskier street crossing decisions overall, but particularly at the delayed time point.

Two supplemental repeated measures GLMs were conducted to evaluate the influence of cognitive factors– perceptual speed and fluid intelligence/spatial reasoning– on risk assessment. All two- and three-way interactions were eliminated from the model if not significant. These models were evaluated after correction for multiple comparisons. Here, I expected adults with lower cognitive performance in each of the two domains to show greater risk in their decision-making. I also expected a compounded effect in adults with worse cognitive performance, greater WMH burden and lower physical function.

CHAPTER 6

RESULTS

6.1 Principal Components Analyses

6.1.1 Physical function

A PCA including the scores for stair ascent and descent, chair stands, 8-foot-up-and-go, and right leg stand loaded onto one general lower extremity physical function factor at the pre and post time points separately (all loadings $\geq .445$; see Table 1). The pre and post factors accounted for 54.05% and 57.80% of variance, respectively. Given the direction of variable loadings, lower factor values indicated better mobility and all values improved to some degree at post-test.

	Pre Factor	Post Factor
Stair Climb Down	.809	.858
Stair Climb Up	.875	.890
Chair Stand	-.645	-.648
8-Foot-Up-And-Go	.817	.821
Right Leg Stand	-.445	-.518

Table 1: Factor loadings for pre and post physical function factors.

6.1.2 Cognition

A PCA with varimax rotation on the cognitive task scores listed in Appendix A loaded onto four components at both pre- and post-testing. Together they explain 67.74% of the variance in these variables at pre (see Table 2 for loadings) and 66.29% of the variance at post (see Table 3 for loadings).

	Fluid Intelligence/ Spatial Reasoning	Vocabulary	Speed	Episodic Memory
Spatial Working Memory	.301	.156	.463	.124
Digit Symbol Substitution	.131	.089	.837	.224
Pattern Comparison	.264	.057	.791	.029
Letter Comparison	.030	.145	.864	.065
Word Recall	-.024	.293	.221	.788
Logical Memory	.231	.363	.131	.696
Paired Associates	.217	.110	.074	.831
Shipley Abstraction	.468	.546	.364	.242
Task Switch Mix Switch	.402	.056	.356	.270
Form Boards	.682	.247	.246	.004
Letter Sets	.465	.500	.368	.168
Matrix Reasoning	.632	.332	.223	.252
Paper Folding	.774	.135	.040	.190
Spatial Relations	.846	.188	.162	.030
WAIS Vocabulary	.124	.862	.162	.256
Picture Vocabulary	.336	.779	.066	.117
Synonym/Antonym	.188	.828	.059	.260

Table 2: Pre-intervention factor loadings for fluid intelligence/spatial reasoning, vocabulary, perceptual speed, and episodic memory cognitive factors

6.2 Analysis 1: Baseline relationship between WMHs and physical function

In a regression framework, greater WMH volume marginally predicted worse baseline physical function (β = .127, t = 1.901, p = .059). However, accounting for age, sex, and cardiovascular disease history attenuated the relationship (β = .053, t = 767, p = .444). After first entering demographics and WMH volume into the model, both greater gait self-efficacy (β = -.396, t = -6.137, p = .000) and greater VO_2 max (β = -.408, t = -7.110, p = .000) at baseline significantly predicted better baseline physical function. See Table 4 for full model results.

Similar regression models were utilized with individual measures of physical function in the place of the factor score. WMH volume did not significantly predict any individual lower extremity physical function measures (ps ¿ .270).

	Fluid Intelligence/ Spatial Reasoning	Vocabulary	Speed	Episodic Memory
Spatial Working Memory	0.416	0.142	0.372	0.101
Digit Symbol Substitution	0.200	0.081	0.832	0.189
Pattern Comparison	0.187	0.089	0.804	0.121
Letter Comparison	0.063	0.184	0.821	0.083
Word Recall	0.218	0.170	0.137	0.816
Logical Memory	0.189	0.366	0.141	0.678
Paired Associates	0.074	0.233	0.151	0.802
Shipley Abstraction	0.476	0.487	0.353	0.314
Task Switch Mix Switch	0.455	0.028	0.323	0.330
Form Boards	0.675	0.175	0.206	0.040
Letter Sets	0.505	0.512	0.289	0.167
Matrix Reasoning	0.560	0.412	0.258	0.204
Paper Folding	0.786	0.125	-0.004	0.232
Spatial Relations	0.803	0.201	0.087	0.056
WAIS Vocabulary	0.184	0.841	0.165	0.219
Picture Vocabulary	0.331	0.808	0.066	0.156
Synonym/Antonym	0.091	0.806	0.083	0.275

Table 3: Post-intervention factor loadings for fluid intelligence/spatial reasoning, vocabulary, perceptual speed, and episodic memory cognitive factors.

	Variables	R^2 change	F change (df)	Sig F change
Level 1	Age, sex, cardiovascular disease	.102	1.436 (3,192)	.247
Level 2	WMH volume	.003	.589 (1,191)	.444
Level 3	Gait self-efficacy, fitness	.306	49.619 (2,189)	.000

Table 4: Stepwise linear regression results with the baseline lower extremity physical function factor entered as the dependent variable.

6.3 Analysis 2: Longitudinal assessment of change in WMH and physical function, and possible intervention group differences

6.3.1 Change in WMH volume

A repeated measures GLM was used to assess change in WMHs over the six-month intervention and group differences therein. Total WMH volume significantly decreased over the

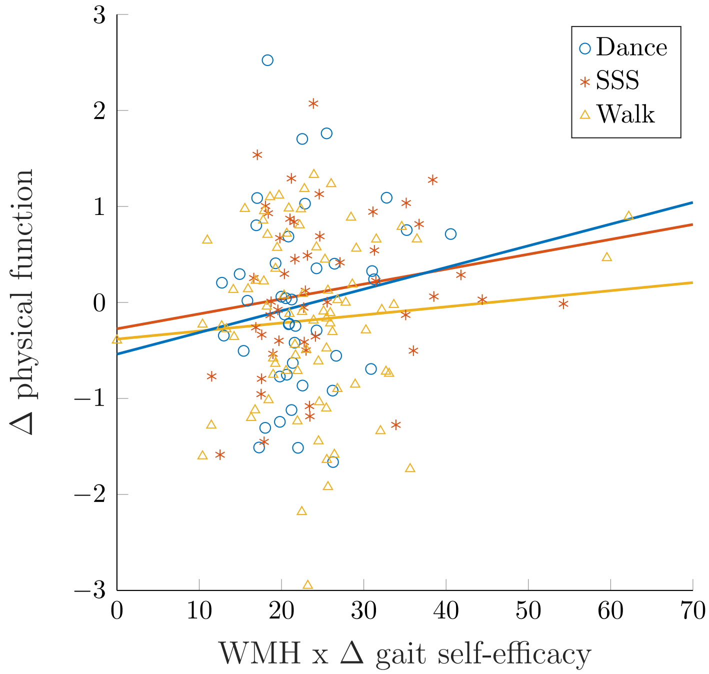

Figure 3: Graph of standardized change in physical function x baseline WMH volume x change in VO_2 max intervention with separate lines for intervention groups.

six-month intervention (F (1,182) = 17.399, p = .000), but this effect did not remain significant after accounting for age, sex, and cardiovascular disease (F (1,177) = 2.307, p = .131). Also, change in WMH volume did not vary by intervention group (F (2,177) = .588, p = .557).

6.3.2 Equivalency at Pre-Intervention

A one-way ANOVA was used to evaluate baseline differences between the three intervention groups at baseline. The three intervention groups did not differ in baseline WMH volume (F (2,221) = 1.441, p = .239), age (F (2,244) = 1.127, p = .326), sex (F (2,244) = .164, p = .849), or cardiovascular history (F (2,244) = 1.257, p = .289). Because these measures did not vary between intervention groups, they were not included as covariates in the following analyses.

6.3.3 Longitudinal Analyses: Predictors of changes in physical function

A univariate GLM was used to assess predictors of change in physical function. Because WMH volume did not change over the intervention period and groups were similar in this measure, pre-intervention WMH volume was included to predict individual differences in change in physical function. Program adherence did not significantly predict change in physical function (= -.077, t = -1.105, p = .270) and was not included in any further models.

Pre-intervention gait self-efficacy and VO_2 max were included as possible predictors of change. Intervention groups were similar in the magnitude of change in physical function (F (2,167) = 2.070, p = .129). In all participants, lower baseline WMH volume (F (1,167) = 10.717, p = .001), greater gait self-efficacy (F (1,167) = 10.209, p = .002), and greater VO_2 max (F (1,167) = 10.211, p = .002) significantly predicted greater gains in physical function over the six-month intervention. The final model (adjusted R^2 = .074) included 2- and 3-way interactions of baseline WMH volume, gait self-efficacy, and VO_2 max. Adults who experienced greater improvement in physical function had lower WMH volume and better gait self-efficacy (F (1,167) = 10.453, p = .001), lower WMH volume and greater VO_2 max (F (1,167) = 10.582, p = .001), better gait self-efficacy and greater VO_2 max (F (1,167) = 9.916, p = .002), and a combination of lower WMH volume, better gait self-efficacy and greater VO_2 max (F (1,167) = 10.354, p = .002) at baseline. Table 5 includes the Pearson correlations to decompose these interactions.

	WMH volume	Gait self-efficacy	VO_2 max
Standardized physical function change	.084 (.249)	-.063 (.377)	-.215 (.002) *
WMH volume		-.103 (.145)	-.196 (.004) *
Gait self-efficacy			.207 (.002) *

Table 5: Pearson correlation of standardized physical function change and baseline WMH volume, gait self-efficacy, and VO2 Max. Values reported include r (p). * indicates significant correlation.

An additional univariate GLM was conducted to evaluate changes in gait self-efficacy and VO_2 max along with baseline WMH as predictors of change in physical function (final model adjusted R^2 = .050). Changes in gait self-efficacy and VO_2 max did not predict change in physical function (Δ gait self-efficacy: F (1,156) = .849, p = .358; Δ VO_2 max: F (1,156) =

.598, p = .441). Overall, groups differed in the relation between change in gait self-efficacy and change in physical function (F (2, 156) = 4.782, p = .010). No significant relationships emerged in post-hoc testing comparing the Dance group with the Walk (Fisher Z = -1.120; p = .263) and SSS groups (Fisher Z = -1.23; p = .219). The Walk and SSS groups also were not significantly different (Fisher Z = .025, p = .803). Consistent with the previous model, standardized change in physical function did not vary by intervention group (F (2,156) = 1.162, p = .316). When accounting for concurrent change in gait self-efficacy and fitness, baseline WMH no longer significantly predicted change in physical function (F (1,156) = 1.076, p = .301).

Finally, intervention groups differed in the complex interaction: change in physical function baseline WMH volume change in gait self-efficacy (F (3,156) = 2.903, p = .037; see Figure 3). Separate two-level stepwise linear regressions for each intervention group were used to decompose this interaction. The first level included baseline WMH volume, change in gait self-efficacy, and change in VO_2 max. The second level included the interaction of baseline WMH volume and change in gait self-efficacy. This interaction term was significant for the Dance group (see Table 6; β = -.316, t = -2.929, p = .006), where adults who either had less baseline WMH volume and/or greater improvement in gait self-efficacy had greater improvement in physical function over the six-month intervention. However, the interaction term was not significant for the SSS or Walk groups (p's > .517).

	Variables	R^2 change	F change (df)	Sig F change
Level 1	Age, sex, cardiovascular disease	.109	7.859 (3,192)	.000
Level 2	WMH volume x gait self-efficacy interaction	.003	.589 (1,191)	.444

Table 6: Stepwise linear regression results for the Dance group decomposing the change in physical function x baseline WMH volume x change in VO_2 max intervention that varied by group.

6.4 Analysis 3: Cognitive applications of WMHs and physical function- Virtual street crossing

6.4.1 Virtual street crossing performance

A 2-level repeated measures GLM was used to assess differences in success between distraction conditions. Adults were less successful in the phone (mean success ratio = .78) compared with the no distraction condition (mean success ratio = .81; F (1,168) = 12.2, p = .001). Age, sex, and cardiovascular health attenuated this difference (F (1,165) = 001, p = .971). Interestingly, participants with greater cardiovascular disease history performed worse on the street crossing task during the phone condition compared with no distraction condition (F (1,165) = 5.123, p = .025). Also, older adults as measured by the continuous age variable (F (1,165) = 9.896, p = .002) and women (F (1,165) = 6.113, p = .014) tended to be less successful overall (mean success = women: .76; men: .83).

A 2 (Distraction) 2 (Lane) repeated measures GLM was used to evaluate possible predictors of virtual street crossing risk assessment measured with TTC. There was no significant difference between the phone and no distraction conditions (F (1,169) = .354, p = .553), thus TTC values were collapsed between these conditions. A one-way ANOVA confirmed that risk assessment did not vary by sex (p's > .136) and thus it was removed from further analysis. Walking speed on the manual treadmill while crossing the virtual street may confound street crossing risk assessment, thus crossing duration was included as a control variable in these analyses.

Assessment of delayed risk (mean TTC exit = 2.593 s) was worse than immediate risk (mean TTC enter = 4.258 s; F (1,169 = 5789.781, p = .000), even when accounting for age, cardiovascular disease history, crossing duration, and baseline physical function (F (1,130) = 6.061, p = .015). Older adults with worse physical function (F (1,130) = 8.522, p = .004), who had more cardiovascular health concerns (F (1,130) = 8.566, p = .004) and greater WMH volume (F (1,130) = 7.728, p = .006), exhibited greater risk (shorter TTC) when exiting the virtual street. This was independent of older adults walking slower, which lead to greater risk when exiting the street (F (1,130) = 10.027, p = .002). Furthermore, older adults with worse physical function and greater cardiovascular health history had greater risk when exiting the street (F (1,130) = 8.763, p = .004).

In general, older adults made riskier decisions (F (1,130) = 12.539, p = .001), and this was in part related to greater history of cardiovascular disease (F (1,130) = 5.832, p = .017) and greater WMH burden (F (1,130) = 4.878, p = .029). However, on average, participants demonstrated greater delayed street crossing risk when exiting the second lane than when entering the street. Because the task required crossing the two street lanes without stopping, a successful attempt required the participants to successfully evaluate both immediate risk at entry and delayed risk when exiting. Adults with worse physical function who spent more time crossing the street demonstrated greater risk at exit than at entry (F (1,130) = 7.370, p = .008), as did individuals with worse cardiovascular health history, worse physical function, and greater WMH burden (F (1,130) = 7.052, p = .009). Interestingly, although worse cardiovascular health history correlated with worse physical function (r = .205, p = .001), it did not significantly correlate with WMH volume (r = .041, p = .546). Thus, older adults may be able to better assess street crossing risk regardless of their physical capabilities for an immediate outcome in the entry lane, but not for delayed outcomes when exiting at the far lane.

6.4.2 Cognitive correlates of virtual street crossing risk assessment

Two supplemental repeated measures GLMs were used to examine the influence of relevant cognitive measures on virtual street crossing risk assessment. These models were identical to the one previously reported, with the addition of the two cognitive factor scores: perceptual speed and fluid intelligence/spatial reasoning. To correct for multiple comparisons, analyses were held to a Bonferroni correction of $p \leq .025$.

The first model included perceptual speed as a predictor. There was no significant difference between immediate versus delayed risk assessment in this model (F (1,106) = .179, p = .673), nor did risk assessment vary by lane as a factor of perceptual speed (F (1,106) = 1.757, p = .188). However, better perceptual speed marginally predicted lesser risk (F (1,106) = 3.096, p = .081) and longer crossing duration significantly predicted greater risk (F (1,106) = 8.644, p = .004) overall.

The second supplemental model included fluid intelligence/spatial reasoning. Risk assessment did not vary by lane as a factor of fluid intelligence/spatial reasoning (F (1,104) = .407, p = .525). Lower score on the fluid intelligence/spatial reasoning factor significantly predicted greater overall risk (F (1,104) = 5.460, p = .021), as did longer crossing duration (F (1,130) = 12.858, p = .001). Furthermore, adults with worse fluid intelligence/spatial reasoning who were older (F (1,104) = 5.471, p = .021), had worse physical function (F (1,104) = 12.131, p = .001), and those who had worse physical function and crossed the street slower (F (1,104) = 13.826, p = .000) exhibited greater risk overall when crossing the street.

Finally, the role of the physical intervention and longitudinal change in cognition and risk assessment were assessed in a two-way repeated measures ANOVA. Standardized change in both speed and fluid intelligence/spatial reasoning factors were included as predictors in the model. In this model, overall risk assessment did not change from pre to post- intervention (F (1, 114) = .077, p = .783), nor did change in risk assessment over time vary by group (F, 1,114) = 2.129, p = .124). There was a significant time x group x fluid intelligence/spatial relationship (F (2,114) = 4.276, p = .016); participants in the Walk group who had greater improvement in fluid intelligence exhibited better risk assessment following the intervention compared with the Dance (z = 1.91, p = .028) but not the SSS groups (z = 1.05, p = .147). The difference between the Dance and SSS groups was not significant (z = -.77, p = .221). The effect did not remain significant when held to a correction for multiple comparisons.

CHAPTER 7

DISCUSSION

The analyses reported here examined the multifaceted relationships between WMHs and lower extremity physical function before and after a six-month aerobic physical activity intervention, as well as the role of these factors in real-world risk taking behavior.

7.1 Analysis 1: Baseline relationship between WMHs and physical function: Unexpectedly weak baseline relationship between WMH volume and physical function

In this sample, the baseline relationship between WMH volume and lower extremity physical function was weak and attenuated by age, sex, and cardiovascular disease history. Researchers have reported WMH volume as a predictor of various lower extremity physical function and falls risk measures (Callisaya et al., 2013; Moscufo et al., 2012; Rosano et al., 2010; Baezner et al., 2008; Srikanth et al., 2008, 2010; de Laat et al., 2011). Given the number of previous studies demonstrating a relationship between WMH volume and various measures of physical function, I hypothesized this sample would display a similar relationship. However, the weak relationship observed between WMH volume and physical function that was substantially attenuated by demographic variables, did not support this hypothesis.

This contradiction might be a result of sample selection. The sample included in this study consisted of relatively young older adults (mean age = 65) who were carefully screened for concomitant health risks. Whereas sample selection for health ensures the effects of interest are not confounded, it results in less variability in WMH burden and lower extremity physical function compared to studies with older and less healthy samples (Callisaya et al., 2013; Rosano et al., 2010; Murray et al., 2010; de Laat et al., 2010; Whitman et al., 2001; Silbert et al., 2008). Additionally, more age-related WM deterioration and greater WMH volume relate to greater deficits in physical functions (Tseng et al., 2013; Bolandzadeh et al., 2014).

This may be another aspect in which this sample lacked the range of performance necessary to observe relationships similar to those previously reported.

Another possible explanation is that in similar samples of relatively young older adults with fewer WMHs, the location of those WMHs may be more relevant. Despite ample research that overall WMH volume relates to physical function (Srikanth et al., 2008; Rosano et al., 2006; Baloh et al., 2003; Baezner et al., 2008; Callisaya et al., 2013), in this sample, gross WMH volume may not have been a sensitive enough indicator of this age-related deterioration to strongly associate to physical function. Some studies have suggested the link between WMH volume and physical function lies specifically in the disruption of tracts that link motor function and executive control (Srikanth et al., 2010; Moscufo et al., 2011; Koo et al., 2012; de Laat et al., 2010). Future work should explore the location and progression of these early stage WMHs using automated segmentation, available with FLAIR images, along with physical functioning assessments at multiple time points over many years.

The results further demonstrated that gait self-efficacy and aerobic fitness were stronger predictors of the physical function factor than any of the demographic variables or WMH volume. Previous studies have reported similar relationships between measures of lower extremity physical function with fitness (Misic, Rosengren, Woods, & Evans, 2007; DiPietro, 2001) and gait self-efficacy (Feltz & Payment, 2005; Seeman & Chen, 2002; T. Liu-Ambrose et al., 2010). Self-efficacy can be a powerful social cognitive tool in shaping expectations and outcomes, particularly those related to physical function (Bandura, 2004; McAuley et al., 2006; Seeman & Chen, 2002; Feltz & Payment, 2005). In this study, the relationship between physical function and cognitive control may indicate less WM deterioration in regions of the brain key to those processes. This would again suggest that clarifying the location of WMHs might be necessary to observe links with physical function in younger and healthier older adults without widespread WM deterioration.

7.2 Analysis 2: Longitudinal assessment of change in WMH and physical function, and possible intervention group differences

7.2.1 Short-term WMH progression

Surprisingly, over the six-month span of the intervention, WMH volume generally decreased regardless of group assignment. However, that change was attenuated by age, sex, and cardiovascular disease history. This diminished change supports my hypothesis that there would not be a significant alteration in WMH volume over the intervention. WMHs are a gross indication of WM deterioration that develop slowly over years. As such, studies evaluating the progression of WMHs, with or without a corresponding intervention, have followed participants for a minimum of a year (Bolandzadeh et al., 2015) and often longer (Moscufo et al., 2012; Callisaya et al., 2013; Whitman et al., 2001; Silbert et al., 2008; Baezner et al., 2008).

Thus, any significant increase or decrease in WMH volume observed across six months is likely a result of methodological constraints, possibly including the 4-mm-thick image slices that were manually masked for WMHs. This measurement technique provided an acceptable estimate for total WMH volume but may not have been ideal for investigating short-term changes. Despite these potential constraints, additional analyses tested individual differences in physical function change, which was not dependent upon changes in WMH.

7.2.2 WMH, gait self-efficacy and VO_2 max predict change in physical function over six months regardless of intervention group

The main longitudinal analysis focused on predictors of physical function change across the intervention. Although given pre-existing literature concerning the benefits of aerobic walking I hypothesized the greatest benefit would be derived from the Walk group, standardized change in physical function did not significantly vary by intervention group. I also hypothesized that baseline values of greater WMH volume, lower gait self-efficacy and lower fitness would predict greater change in physical function. However, the opposite trend held true as participants with lower WMH volume, better gait self-efficacy, and greater VO_2 max at baseline saw the greatest benefit to physical function over the six months.

Studies have concluded that lower cardiorespiratory fitness contributes to blunt white matter vascular pathology, including WMHs (Ahlskog et al., 2011; Voss et al., 2013) and deteriorating physical function (DiPietro, 2001; Misic et al., 2007). Thus, I expected an intervention that improves aerobic health to benefit both brain health and physical function, particularly for individuals already in a state of white matter decline (Paterson & Warburton, 2010; Brach, Simonsick, Kritchevsky, Yaffe, & Newman, 2004). Although there is support in the literature for physical function gains during a six-month intervention in aging samples (McAuley et al., 2013; Nelson et al., 2004), short-term vascular benefits may not be observable in an otherwise healthy sample of relatively young and healthy older adults.

The complex relationships between these variables, both uniquely and in interaction, suggest that healthier older adults had greater physical function improvements with any additional physical activity– aerobic or otherwise. Others have similarly reported benefits from any increase in physical activity in older samples, which may explain the findings presented here (DiPietro, 2001; Etnier, Nowell, Landers, & Sibley, 2006). Understanding these aspects of aging is critical because physical function limitations are often the cause for older adults to lose independence and require institutionalization (von Bonsdorff et al., 2006).

7.2.3 Change in gait self-efficacy and baseline WMH volume interact to predict change in physical function for Dance condition

A second analysis considered the same question, examining standardized changes in gait self-efficacy and VO_2 max in place of their corresponding baseline measures. I hypothesized that individuals with the greatest gains in these measures would likewise experience the greatest gains in physical function but neither of these change scores independently predicted change in physical function. However, Dance group participants with lower baseline WMH volume and/or greater gait self-efficacy improvements experienced greater gains in physical function. This effect was not present in the Walk or SSS groups.

A recent article examined the same samples perceived intensity (i.e., How hard do you feel like you were working?) during the intervention (Ehlers, Fanning, Awick, Kramer, & McAuley, 2016). The Dance condition was intended to engage participants cognitively in learning the dance routines and physically with moderate-to-vigorous activity. Yet, the Dance group reported lower perceived intensity than either the Walk or SSS groups. They also engaged in more out of class aerobic activity than the Walk group (Ehlers et al., 2016). In this case, that extra activity offers a possible confound at play in this sample although it does not account for the null results in the Walk condition.

7.3 Analysis 3: Cognitive applications of WMHs and physical function- Virtual street crossing

7.3.1 Age-related declining vascular health affects virtual street crossing risk assessment

The final series of analyses focused on a virtual "real-world" application to stress the importance of improving lower-extremity physical function. These analyses examined the virtual street crossing task, specifically focusing on individual differences in risk assessment during the task. While previous reports exist of older adults being less successful at crossing a virtual street compared with younger adults and making riskier decisions during distracted street crossing conditions (Neider et al., 2011) the joint influence of brain health, physical function, and cognitive variables has remained unstudied in this context.

As hypothesized, compared with entering the street, the TTC values when exiting the second lane were lower (after overall mean-centering) indicating riskier decisions. This suggests that it is more difficult to guarantee a safe buffer for a delayed versus an immediate scenario. Additionally, as expected, adults who were older, had more cardiovascular disease history, or greater WMH volume made riskier decisions overall- an effect that was stronger in delayed TTC.

Additionally, adults with worse physical function scores, more cardiovascular disease history, and greater WMH volume made more conservative safety decisions when entering the street but their delayed risk assessment was consistently worse. Predictive forecasting of risk requires acquiring more information from the traffic and greater planning to get across both lanes, making it inherently more challenging. These relationships imply an underlying cognitive component to the risk assessment measure, especially given that the relationship is significant after accounting for gait speed.

To successfully cross the street, an individual must judge the speed of traffic and adjust their walking speed (Butler et al., 2016; Oxley, Ihsen, Fildes, Charlton, & Day, 2005), a task with both physical and cognitive elements. In this case, adults who suffer from worse physical function or vascular health seemed to compensate in their immediate judgments, leaving more time to cross the first lane, but that did not translate to better predictive or delayed risk assessment.

Over 50,000 older adults are treated in emergency rooms annually for non-fatal pedestrian injuries (Naumann, Dellinger, Haileyesus, & Ryan, 2011). Naumann and colleagues reported that of those injuries, 77% were related to falling, a common result of physical function impairment in aging (Bridenbaugh & Kressig, 2015; Hsu et al., 2012). Therefore, interventions geared at bettering older adults physical function may directly translate to improving pedestrian safety.

7.3.2 Better cognitive performance translates to less overall pedestrian risk

Finally, I examined potential cognitive correlates of risk assessment in the virtual street crossing paradigm. As hypothesized, adults who performed better on cognitive tasks, specifically in perceptual speed and fluid intelligence/spatial reasoning domains, made generally less risky street crossing decisions. Moreover, adults who had better fluid intelligence/spatial reasoning and better lower extremity physical function (measured both by physical function factor or crossing duration) also made less risky crossing decisions.

Thus, while cognition does have some influence on overall risk assessment in this virtual paradigm, perceptual speed and fluid intelligence/spatial reasoning did not aid in the deficit older adults experience particularly when assessing delayed risk. Tournier and colleagues (2016) briefly reviewed the literature on age-related deficits in cognition and physical function and subsequent effects on pedestrian safety. They made recommendations for improving older adult pedestrian risk taking such as training programs and better-placed, safer crosswalks. These suggestions, along with interventions to improve physical functions, are feasible steps to lessen risky pedestrian behaviors in older adults.

Several inherent limitations may have influenced these findings including the health and mean age of the sample, less-than-ideal WMH volume measurement, and the short duration of the intervention. A longer intervention may be needed for elderly people with gross white matter decline to exhibit progression of WMHs and explore the resulting relationship with lower extremity physical function. However, in this study, a sample of formerly sedentary, relatively young older adults who were healthiest (with lowest WMH volume, greatest gait self-efficacy, and greatest VO_2 max at baseline) showed the greatest gains in lower extremity physical function regardless of type of physical activity they engaged in over a six-month period.

7.4 Conclusions and future directions

This dissertation contributes to the extant literature in several ways. Whereas the progression of WMHs over the course of years has been documented, less was known about the individual differences of baseline WMH burden on physical function gains across an aerobic physical activity intervention. These dissertation analyses also translate laboratory measures to real-world applications relevant to older adult safety and independence.

APPENDIX A

COGNITIVE TASKS

Task	Description	Cognitive Domain
Spatial Working Memory	computer-based, identify if a red dot appears in the same location as a previous series of black dots	Working Memory
Task Switching	computer-based, randomly switch between completing two trained tasks	Cognitive flexibility
Matrix	computer-based, identify the missing portion of a pattern	Fluid Intelligence
Shipley Abstraction	paper-based, complete a sequence with appropriate letter or number	Fluid Intelligence
Letter Sets	paper-based, identify which of 5 sets of letters does not follow the pattern	Fluid Intelligence
Spatial Relations	computer-based, determine which shape is made from an unfolded pattern	Spatial Reasoning
Paper Folding	computer-based, determine the set of holes created by paper that was folded and hole-punched	Spatial Reasoning
Form Boards	computer-based, determine shapes necessary to fill a space	Spatial Reasoning
Digit Symbol Substitution	paper-based, use a key to identify which symbol corresponds with each digit	Perceptual Speed
Letter Comparison	paper-based, compare strings of letters and identify if they are the same or different	Perceptual Speed
Pattern Comparison	paper-based, compare patterns and identify if they are the same or different	Perceptual Speed
Paired Associates	computer-based/experimenter, recall second word from word-pairs	Episodic memory
Word Recall	computer-based/experimenter, recall as many words as possible from a list across 4 trials	Episodic memory
Logical memory	computer-based/experimenter, recall details from a story	Episodic memory
Synonym/Antonym	computer-based, choose word that is the synonym/antonym of the target word	Vocabulary
Picture Vocabulary	experimenter-administered, give appropriate name of each pictured item	Vocabulary
WAIS vocabulary	experimenter-administered, verbally give the definition of a series of words	Vocabulary

Appendix A: Complete list of cognitive tasks

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