THE EFFECTS OF EXERCISE TRAINING ON COGNITIVE RESERVE AND COGNITIVE FUNCTION IN HEALTHY OLDER WOMEN

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THE EFFECTS OF EXERCISE TRAINING ON COGNITIVE RESERVE
AND COGNITIVE FUNCTION IN HEALTHY OLDER WOMEN

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Dedication

To Mom & Dad
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Abstract

Cognitive reserve theory suggests that physical activity may protect individuals from cognitive decline. At the brain level, greater cognitive reserve may manifest as greater neural network efficiency. Our purpose was to investigate 1) whether participation in a 16-week walking program increased brain efficiency, and 2) whether increased brain efficiency correlated with change in fitness and task performance. Our secondary purpose was to investigate whether exercise training improved performance on a battery of cognitive tasks, particularly executive functioning performance. Seventeen healthy but sedentary women aged 60-75 years participated in a supervised walking program; eighteen women served as a non-randomized control group. Twelve women in the intervention group underwent fMRI scanning at baseline and post exercise training.

During fMRI scanning, participants (mean age 63 years) completed a working memory task (Sternberg delayed-match-to-sample letter task). Participants showed a greater capacity to recruit task-related brain regions after exercise training (indicated as greater BOLD signal). These regions included left inferior frontal gyrus, left cuneus, right rolandic operculum, left middle temporal gyrus, left postcentral gyrus, left superior med frontal, left superior frontal gyrus, right caudate, right inferior temporal gyrus (ps < 0.001). No task-related brain regions were utilized more efficiently after exercise training (ps > 0.001). These findings suggest that exercise-induced cognitive reserve may present as a greater ability to recruit neural resources, rather than greater brain efficiency, in this sample. As there were no significant correlations between changes in task-related
brain activation and changes in performance (reaction time slope) with exercise training (r values < 0.49), these findings should be interpreted with caution.

A slightly larger sample of intervention participants (n=17; mean age 64 years) completed a battery of cognitive tasks (CANTAB®) before beginning and after completing exercise training; a matched control group of participants (n=18; mean age 66) completed the battery on dates approximately 16 weeks apart. Based on ANOVA analyses utilizing residualized change scores, there were no significant differences between the groups on any cognitive performance measures (ps > 0.24). Due to the small sample size, we also calculated effect sizes. Effects of the exercise intervention were small for the total trial and total error outcomes on the paired associate learning task (d=0.20 and d=0.39, respectively), as well as for the spatial span task (d=0.38). For the control group, effect sizes were small for the verbal free recall task (d=0.23), medium for the rapid visual processing (d=0.62) and paired associate learning task (d=0.71 and d=0.52 for the total trial and total error outcomes, respectively), and large for the spatial span task (d=1.02). These findings are unexpected, but plausible explanations have been realized and are discussed.
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Chapter 1: Introduction

As the baby boomers continue to enter older adulthood, the incidence of Alzheimer’s disease (AD) is becoming a pressing public health concern. In a time when there is no effective treatment for AD, cognitive reserve (CR) theory suggests that a physically and mentally active lifestyle may help older adults stave off AD symptoms (i.e., the dementia) (Stern, 2006). Originally developed to explain the discordance between clinical symptoms of AD and severity of AD pathology upon autopsy, CR theory posits that ‘building’ CR by leading an active lifestyle allows an individual’s brain to become more efficient, more flexible and/or more capable of recruiting necessary resources. The idea is that neural networks or circuits that are functioning in this manner are more difficult to disrupt, and therefore individuals with more CR should be better able to maintain their cognitive function despite, for example, advancing AD pathology. Importantly, it is believed that individuals can continue to build their CR throughout life; it is never too late to start.

According to Stern, the neural implementation of CR can be subdivided into two components: neural reserve and neural compensation. Neural reserve refers to the efficiency, capacity or flexibility of brain networks subserving cognitive functions in the healthy brain. Neural compensation refers to the ability to use alternative brain networks when original networks are damaged (Stern, 2009). Stern has devised a systematic approach to testing these mechanisms using functional magnetic resonance imaging (fMRI). The approach is based on the assumption that differences in task-related brain
activation can provide insight into the neural implementation of CR; differences can be examined across groups of individuals (e.g., young versus old) or within a group of individuals as a function of some proxy variable of mental activity (e.g., years of education).

The within-subjects approach can be used to study the neural implementation of CR in the older adult brain. This approach, in essence, uses increasing cognitive demands to mimic the challenge created by pathology. When using this approach, greater neural network efficiency may be expressed by lesser increases in network activation (within the same network) when switching from low to high-demand conditions. Alternatively, greater neural network capacity may be expressed as greater increases during this switch, serving as evidence of the brain’s greater ability to recruit neural resources when facing a cognitive challenge. Research suggests that neural reserve in the older adult brain is more likely to manifest as greater efficiency than greater capacity (Scarmeas et al., 2003; Stern et al., 2005). Greater CR in the older adult brain can also be reflected in the ability to use compensatory resources (i.e., different or additional brain regions) in the face of increasing cognitive demands.

The role of physical activity in building CR has been understudied. There is a growing body of neuroimaging research showing that the brain of a fit or physically active person functions differently (and presumably better) than the brain of an unfit or sedentary person (Colcombe et al., 2006; Colcombe et al., 2004; Erickson et al., 2009; Erickson et al., 2011; Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012; Voss et al., 2010a; Voss et al., 2010b). Additionally, evidence from prospective epidemiological studies has demonstrated that physical activity delays the onset of cognitive decline and
incidence of dementia (Physical Activity Guidelines Advisory Committee, 2008), and reduces the risk of AD (Hamer & Chida, 2009). Randomized controlled trials complement these findings, suggesting that exercise training can improve or maintain cognitive function in the short term (Colcombe & Kramer, 2003). Neuroimaging studies using Stern’s approach could help unveil the mechanisms responsible for AD risk reduction with higher levels of physical activity and, in doing so, help bolster exercise and physical activity promotion as a non-pharmacological means of addressing the rising incidence of AD.

Scope

This project examined the neural basis of exercise-induced CR in healthy older women using fMRI. The relationship between CR and cognitive performance was examined. In a separate study, the relationship between exercise training and cognitive performance was examined, irrespective of changes in CR.

Aims

1. To determine whether participation in an exercise training program builds CR, evidenced by greater efficiency in a task-related brain network.

2. To determine whether participation in an exercise training program improves cognitive performance.

Hypotheses

Aim 1

1.1. Relative to baseline, it was hypothesized that there would be a smaller difference in task-related neural network activation during low versus high-demand working memory trials after completion of a 16-week exercise
program. Changes in task-related activation were expected in premotor, parietal, inferior frontal and middle frontal areas (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007).

1.2. It was hypothesized that greater improvement in fitness would correlate with greater improvement in efficiency in the working memory network.

1.3. It was hypothesized that greater efficiency in the working memory network would correlate with better performance (i.e., lesser reaction time slope).

Aim 2

2.1. It was hypothesized that participation in a 16-week exercise program would improve sustained attention, visuospatial learning, spatial working memory, and verbal free recall, as compared to no exercise; the greatest differential between groups was expected on tasks that challenge executive function capabilities (i.e., spatial span, rapid visual processing).

2.2. It was hypothesized that greater improvement in cognitive performance would correlate with greater improvement in fitness.
Chapter 2: Review of the Literature

Public Health Impact of Aging and Dementia (Alzheimer’s type)

In the year 2010, 40 million Americans were 65 years or older, representing 13.1% of the population. As the baby boomer generation continues to age that number is projected to balloon to 72.1 million, or 19.3% of the population, by 2030 (U.S. Department of Health and Human Services, 2011). The astonishing rate at which our population is aging has pushed the prevention and treatment of dementias to the forefront of the public health agenda. Alzheimer’s disease (AD) is by far the most common type of dementia, accounting for 60-80% of cases. It is also deadly; AD is the fifth leading cause of death in older adults. The latest report from the Alzheimer’s Association indicates that 1 in 3 older adults in the United States dies with AD or another dementia (Alzheimer's Association, 2014).

It is estimated that 1 in 9 Americans over the age of 65 years (11%) and 1 in 3 over the age of 85 years (32%) have AD; because women live longer than men, almost two thirds of AD cases are women. The economic impact of AD and other dementias is tremendous; in 2013, an estimated $203 billion was spent on health care, long-term care, and hospice care for individuals with AD and other dementias, with about 70% of the costs being covered by Medicare and Medicaid. By 2050, the annual incidence of AD is expected to double, and costs of care are expected to reach $1.2 trillion. In addition to these unprecedented financial costs, Americans provided 17.5 billion hours of unpaid care to persons with AD in 2012. This high level of caregiving presents its own public
health issue, as the stress of caring for a loved one with AD can have detrimental effects on the mental and physical health of the caregiver (Alzheimer's Association, 2014).

There is currently no effective treatment for AD, making prevention efforts critical. Researchers now know that pathological changes in the brain may begin more than two decades before AD symptoms present (Alzheimer's Association, 2014). With this knowledge, we know that it already too late to prevent the onset of AD pathology in the aging baby boomers. Luckily, although Alzheimer’s disease cannot be stopped, it is still possible that Alzheimer’s dementia can be. The cognitive reserve (CR) theory posits that certain exposures during life, such as mental and physical activity, may improve the brain’s ability to cope with damage. Thus, until scientists find ways to detect the disease in asymptomatic individuals and intervene effectively, prevention efforts with cognitively intact older adults, or even middle-aged adults, might focus on building CR. The tenets of CR theory serve as the basis of the current proposal.

**Healthy Cognitive Aging: Changes in Brain & Behavior**

Dementia is not an inevitable or normal part of aging. In non-pathological aging, some cognitive functions do decline, but others remain remarkably intact. For example, emotional processing, autobiographical memory and automatic memory remain stable, but processing speed, working memory and episodic memory encoding tend to decline with age (Hedden & Gabrieli, 2004). Both cross sectional and longitudinal studies suggest that these declines occur, but there is disagreement as to whether they occur gradually throughout adulthood or begin declining in late middle age (Hedden & Gabrieli, 2004). Alternatively, there is consensus that well-practiced and/or knowledge-related cognitive functions, such as short term memory, vocabulary, and semantic knowledge,
decline more sharply after an individual reaches older adulthood (although it is unclear whether these late-life declines are related to disease processes) (Hedden & Gabrieli, 2004). The specificity of these behavioral changes (rather than a global decline in function) suggests that some areas of the brain are more affected by the aging process than others. Below I discuss some of the major structural and functional changes that occur in the ‘healthy’ aging brain that may contribute to changes (or stability) in cognitive performance.

Due a gradual reduction in synapses starting in the third decade of life, the aging brain is smaller in volume than the young brain. In line with observable changes in behavior, brain shrinkage is not uniform across regions (Hedden & Gabrieli, 2004). The prefrontal cortex (largely responsible for executive functioning) shows the largest volumetric decline with aging; after age 20, the prefrontal cortex is thought to lose 5% of its volume per decade (Raz et al., 2004). Closely integrated with the prefrontal cortex is the striatum, which also decreases in size with age. Volumetric and neurotransmitter deficits (including reductions in norepinephrine, serotonin, and especially dopamine (Buckner, 2004; Park & Reuter-Lorenz, 2009) in the prefrontal cortex and striatum have been associated with declines in cognitive performance (Hedden & Gabrieli, 2004). There is also a selective effect of aging on white matter, with the greatest changes in white matter integrity occurring in the prefrontal cortex and anterior corpus callosum (Buckner, 2004; Hedden & Gabrieli, 2004; Park & Reuter-Lorenz, 2009). These white matter abnormalities may disrupt the connection between the prefrontal cortex and other brain areas, including the hippocampus (Hedden & Gabrieli, 2004), and have been linked with declines in many domains of cognitive function (including memory and executive
function) (Buckner, 2004). With normal aging, volumetric changes in the hippocampus and surrounding areas are less dramatic than those observed in prefrontal cortex; humans typically lose approximately 2-3% of their hippocampal volume per decade (Raz et al., 2004), and 1% annually after age 70 (Jack et al., 1998). In multiple structural MRI studies, hippocampal volume has been shown to predict memory performance after age 60 (Hedden & Gabrieli, 2004). Additionally, volumetric declines are not uniform across regions of the hippocampus and related medial temporal lobe structures; the entorhinal cortex and CA1 region of the hippocampus appear intact with normal aging, but the dentate gyrus and subiculum shrink (Hedden & Gabrieli, 2004).

In multiple fMRI studies with healthy older adults, dampened activity in the left hippocampus during memory task performance is often observed concurrently with alterations in prefrontal activation (usually increases) (Hedden & Gabrieli, 2004). Multiple theories of cognitive aging suggest that overactivation in the prefrontal cortex is a beneficial compensatory response to normal age-related changes in the brain, including declines in hippocampal function (Cabeza, 2002; Park & Reuter-Lorenz, 2009). The idea that age-related functional changes in these two structures may be tightly linked makes sense from a cognitive standpoint, as executive function and memory function are not independent of one another; a degree of control processing is inherent to remembering (e.g., memorization may require strategic elaboration and retrieval may require a guided search) (Buckner, 2004). Indeed, multiple studies suggest that it is prefrontal cortex function, not medial temporal lobe function, which differentiates high versus low memory performance in older adults (Hedden & Gabrieli, 2004).
Conclusions. Even in the healthiest aged brain, structural and functional changes lead to mild decrements in some aspects of cognitive functioning (e.g., working memory, episodic memory). Subtle memory loss in older adulthood may be largely due to prefrontal cortex-mediated executive function deficits (Buckner, 2004), which is etiologically different than memory loss due to AD (mediated by medial temporal lobe pathology) (Buckner, 2004). Structurally, loss of prefrontal cortex volume is a normal part of aging, while major shrinkage in medial temporal lobe structures tends to be indicative of pathology. There is also a normal decline in frontal white matter integrity, as well as neurotransmitter availability and function (particularly dopamine), with advancing age (Barnhart et al., 2009; Park & Reuter-Lorenz, 2009). Functionally, heightened activity is often found in the prefrontal cortex, while hippocampal activity tends to decline (Hedden & Gabrieli, 2004).

Pathological Cognitive Aging: Changes in Brain & Behavior with AD

Although some subtle changes in cognitive function are normal with advanced age, dementia is defined as disease-related loss of memory and other cognitive functions that interferes with activities of daily living (Jack, 2012). The transitional phase between normal cognitive aging and clinical dementia is known as mild cognitive impairment (MCI) (Jack, 2012). This discussion focuses primarily on AD, the most common cause of dementia; more specifically, the focus is on late onset sporadic AD, which accounts of 95% of AD cases (Alzheimer's Association, 2014).

The most common early symptom of AD is trouble remembering new information; apathy and depression can also occur early on. Other common symptoms include trouble with executive functions (e.g., planning, problem solving), difficulty
completing familiar tasks, confusion with time or place, problems with words in speaking or writing, and trouble understanding visual images or spatial relationships (Alzheimer's Association, 2014). Vascular dementia, caused by microscopic bleeding and vessel blockage, is the second most common type of dementia, and the most likely to co-occur with AD (Alzheimer's Association, 2014). The effects of AD and vascular brain injury appear to be additive (Jack, 2012), and the presence of vascular disease may be the difference between individuals with AD that develop symptoms of dementia and those that do not (Marchant et al., 2013).

**AD Pathology.** The two pathological hallmarks of AD are amyloid-β (Aβ) plaques and tau neurofibrillary tangles. The amyloid cascade hypothesis suggests that dysfunction in the Aβ pathway may be the initial event in AD, or at least one very early in the disease process. Late onset sporadic AD is thought to be a disease of inadequate Aβ clearance; as Aβ builds up, neuritic plaques surrounded by inflammatory cells and neuron fragments form in the neocortex (Jack, 2012). Recent evidence suggests that amyloid plaques are necessary but not sufficient for cognitive decline (Jack, 2012); at autopsy, about 30% of cognitively normal individuals have an accumulation of Aβ plaques sufficient to meet criteria for AD. Importantly, these individuals usually do not have significant tau tangles (Jack, 2012).

Unlike plaques that form in the extracellular space, neurofibrillar tangles result from the intracellular aggregation of tau protein. In the healthy brain, tau protein binds to and supports the microtubules that form the neuronal cytoskeleton; in AD, tau disengages from the microtubules and binds with other tau threads to cause insoluble tangles. Without the support of tau, the cytoskeleton collapses and cell death follows (U.S.
Department of Health and Human Services, 2008). Tau pathology begins in the transentorhinal area and progresses to the hippocampus, eventually reaching neocortical association areas, and lastly primary sensorimotor and visual areas (Braak, 1991; Jack, 2012). A closer association has been found between tau tangles and cognitive impairment than amyloid plaques and cognitive impairment, leading some researchers to argue that therapies should target tau rather than amyloid (Jack, 2012).

**Conclusions.** It can be very difficult to differentiate normal changes in cognitive aging from the slow, gradual onset of AD. Researchers now believe that AD-related changes in the brain may occur more than two decades before the first noticeable symptoms of AD present themselves (Alzheimer's Association, 2014). The deposition of Aβ in the cortex is thought to precede the development of intercellular tau tangles; interestingly, cortical amyloid plaques are found in many non-demented individuals at autopsy (Braak, 1991). The trademark memory impairment associated with clinical AD is due largely to cellular pathology and cell loss in medial temporal lobe structures (Buckner, 2004). These structures (especially the entorhinal cortex, which is key in connecting the hippocampus with other brain regions) are the earliest affected by neurofibrillary tau tangles (Braak, 1991). There are many factors that contribute to dementia risk, and although some are out of our control, others are modifiable. As lifestyle choices may contribute substantially to an individuals’ risk profile (and they inherently lend themselves to intervention), they are the focus of the next section.

**Lifestyle Choices and Dementia Risk**

Although some risk factors for AD cannot be modified (e.g., age, family history, Apolipoprotein E [APoE] genotype), others can be. Many cardiovascular disease risk
factors also increase AD risk, including mid-life obesity, diabetes, high cholesterol and midlife hypertension (Alzheimer's Association, 2014). As many lifestyle choices, such as leading an active lifestyle, eating a healthy diet, and not smoking, are known to lower cardiovascular disease risk, it is logical that they may also affect dementia or AD risk. Other factors, such as engagement in mental and social activities, years of education, and level of occupational attainment, have also been studied in relation to dementia risk. Below I highlight some recent studies and review papers focused on these topics. A subsection focuses exclusively on the role of physical activity in reducing dementia or AD risk. Although cross-sectional studies exist, I review only longitudinal epidemiological studies, as they allow for causal inferences.

In a 2010 review paper, Arab and colleagues discussed Mediterranean diet adherence, supplement intake, and physical activity in relation to dementia or AD risk; although most Mediterranean diet and physical activity studies demonstrated a protective effect, supplement studies were less conclusive (Arab & Sabbagh, 2010). In 2009, Scarmeas et al reported that, when considered simultaneously, both Mediterranean-type diet adherence and physical activity independently reduced the risk of incident AD after an average 5.4 years of follow-up (Scarmeas et al., 2009). In 2012, Norton and colleagues investigated how lifestyle behaviors, specifically diet, exercise, smoking, alcohol consumption, church attendance, and social interaction, cluster together to collectively affect dementia and AD risk (Norton et al., 2012). Four behavioral clustering patterns emerged; ‘unhealthy religious’, ‘unhealthy non-religious’, ‘healthy moderately religious’ and ‘healthy very religious’; the two ‘healthy’ groups (containing individuals who ate a
healthy diet, exercised, stayed socially engaged, and didn’t smoke) had a lower risk of AD. Follow-up averaged 6.3 years.

In 2006, Valenzuela and Sachdev conducted a meta-analysis of 22 longitudinal studies examining mental complexity in relation to incident dementia (Valenzuela & Sachdev, 2006). Most studies used years of education as their measure of ‘behavioural brain reserve’, while some used level of occupational attainment, premorbid IQ, or engagement in mental/social activities. After an average 7.1 years of follow-up, higher brain reserve was associated with a significantly lower risk of incident dementia (OR=.54). In 2012, Paillard-Borg and colleagues conducted a study based on 388 incident dementia cases that developed over a 9-year follow-up period, finding that an ‘active lifestyle’, defined as participation in mental, physical, or social activity, delayed the onset of dementia independent of education, medical condition, APoE genotype and other factors. Additionally, the broader the spectrum of activities an individual participated in, the older the age of dementia onset (Paillard-Borg, Fratiglioni, Xu, Winblad, & Wang, 2012). A 2011 study by James et al focused on the protective effects of social activity, finding that, over an average of 5.2 years of follow-up, the rate of global cognitive decline was reduced 70% in older adults who were frequently socially active compared to those who were infrequently socially active (James, Wilson, Barnes, & Bennett, 2011).

Physical Activity/Exercise and Dementia Risk

Other studies have focused exclusively on the role of physical activity in reducing dementia risk. To date, no randomized controlled trial has focused on dementia onset as the outcome of interest, and thus the strongest evidence directly linking physical activity
and a reduced risk of dementia comes from longitudinal epidemiological studies (Rolland, 2008). In 2008, Rolland and colleagues conducted a systematic review of longitudinal epidemiological studies linking physical activity and risk of cognitive decline, dementia or AD (Rolland, 2008). Relevant studies dated back to 1991, and of the 24 studies reviewed, 20 showed a significant protective effect of physical activity against cognitive decline or dementia. Follow-up periods ranged from 2 to 21 years, and most assessed physical activity as self-reported leisure time physical activity.

Many relevant longitudinal studies have been published since the Rolland review. A 2012 study by Bowen et al found that older adults reporting greater participation in vigorous physical activity (e.g., aerobics, running, heavy housework) in the previous 3-7 years had a lower risk of dementia (Bowen, 2012). In 2012, Buchman and colleagues found that a higher level of total daily physical activity, measured for 10 days with actigraphy, was associated with a reduced risk of AD (average follow-up 4 years) (Buchman et al., 2012). A 2012 study by Middleton et al found that total activity energy expenditure (measured as total energy expenditure measured using doubly labeled water minus resting metabolic rate measured using indirect calorimetry) was related to risk of cognitive impairment at 2 or 5 year follow-up; older adults in the highest sex-specific tertile of activity energy expenditure had the lower odds of declining at least one standard deviation on the Modified Mini-Mental State Examination compared to those in the lowest tertile (Middleton et al., 2011).

A 2008 Italian study by Ravaglia et al provided additional support for the link between physical activity and lower dementia risk, but only for vascular dementia (not Alzheimer’s dementia) (average 4 year follow up) (Ravaglia et al., 2008). Similarly, in
Verdelho et al found that physical activity reduced the risk of MCI and dementia in older adults with vascular cerebral damage (white matter changes), but when dementia criteria were divided further into vascular dementia or AD, only vascular dementia risk was reduced (3 year follow up) (Verdelho et al., 2012).

**Conclusions.** An independent panel at a 2010 National Institutes of Health State-of-the-Science Conference found that Mediterranean diet, folic acid intake, light to moderate alcohol intake, cognitive activity and physical activity were associated with lower risk of AD (Daviglus et al., 2011). Unfortunately, due to methodological limitations (such as reliance on self-report measures and inconsistent use of proper diagnostic criteria) and poor understanding of the course of AD pathology, the panel deemed the level of evidence to be low and ‘insufficient’ to support the use of lifestyle interventions to prevent AD. In the years since the conference was held, researchers have continued the pursuit and improved the evidence base; specific to physical activity, many recent prospective epidemiological studies have shown a reduced risk of dementia with higher levels of physical activity, even after controlling for relevant demographic, genetic, health, and lifestyle factors (Bowen, 2012; Buchman et al., 2012; Middleton et al., 2011).

**Physical Activity/Exercise and Cognitive Function**

Although no randomized controlled trials have looked specifically at incidence of dementia as an outcome, many studies have studied the relationship between exercise and cognitive function in the short term. Below I review exercise trials with older adults. As the focus of this proposal is prevention rather than symptom reversal or treatment, I do not discuss studies in samples with dementia. Studies using neuroimaging technologies to assess brain-level changes with exercise training are also be reviewed; cross-sectional
studies are included in this sub-section, as the use of these technologies in exercise science is relatively new. Plausible mediating and moderating variables of the exercise-cognition relationship are discussed in the final sub-section.

Exercise-cognition research in the 21st century has been heavily informed by the 2003 meta-analysis of randomized controlled trials published by Colcombe and Kramer (Colcombe & Kramer, 2003). This heavily cited landmark paper summarized the evidence of 18 exercise trials conducted with older adults from 1966-2001, verifying a ‘robust but process-specific’ benefit of fitness on cognitive function. An overall effect size of 0.48 was calculated for improvement in all cognitive domains, whereas the effect size was 0.68 for executive control processes. In confirming their previous hypothesis (Kramer et al., 1999) that executive functioning performance benefits most from exercise training, Colcombe and Kramer influenced task selection in many succeeding studies, making executive functioning the most heavily studied cognitive domain in exercise psychology. Other main findings from this landmark meta-analysis include the following: individuals in dual aerobic/resistance training programs improved more than individuals in aerobic training alone; interventions in which more than half the participants were females were more effective than those in which at least half were male; and participants in the mid-old category (66-70) improved most (versus young old [55-65] and old-old [71+]). Of particular relevance to the current proposal, the authors’ suggestion that ‘changes in cognitive performance must be mediated by changes in neural activation’ sparked the use of functional magnetic resonance imaging (fMRI) in exercise psychology research.
Recent studies have confirmed Colcombe and Kramer’s findings in healthy and at-risk populations. In 2008, Lautenschlager and colleagues randomized 170 older adults with MCI or memory complaints to either a 6-month home-based physical activity program (self-directed, mostly walking, 50 min, 3x/wk) or an education and usual care group (Lautenschlager, 2008). After training, older adults in the intervention group had better delayed word recall and performed better on the Alzheimer’s Disease Assessment Scale, which assesses memory, language and praxis; these benefits persisted 12 months after program completion. The authors noted that the observed improvement on the Alzheimer’s Disease Assessment Scale with physical activity compared favorably with the use of donepezil (an acetylcholinesterase inhibitor prescribed for mild to moderate AD) at both 6 and 18 months.

A 2010 study by Baker and colleagues (Baker et al., 2010b) found that a 6-month aerobic exercise program (versus stretching control) improved a number of executive functions (e.g., multitasking, cognitive flexibility, selective attention) but did not improve declarative memory in sedentary older adults with MCI. The executive functioning benefits of exercise were evidenced not only by improvements in the intervention group, but also declines in the control group. In line with findings from the Colcombe and Kramer meta-analysis, many of the effects were greater in women despite similar improvements in cardiorespiratory fitness across genders. In another 2010 study by Baker et al, 28 older adults with glucose intolerance (a risk factor for cognitive impairment and dementia) participated in either 6 months of aerobic exercise or stretching. Again this group found that aerobic exercisers saw improvements in executive functioning (Trails B performance, Stroop interference trial performance, task...
switching and verbal fluency), but not memory performance compared to the control group (Baker et al., 2010a).

Other studies have attempted to maximize cognitive benefits with joint exercise and cognitive training. In 2013, Barnes et al randomized older adults with memory or thinking complaints to a 3-month aerobic exercise or stretching and toning control program (60 min 3d/wk), as well as a 3-month mental activity training or educational lecture control program (60 min 3d/wk); thus, four groups were formed (Barnes et al., 2013). At the end of the study, all four groups improved on a comprehensive neuropsychological test battery, but no group improved significantly more than any other. The authors suggested that the amount of activity might be more important than the type in this population. In a 2012 study by Andresen-Haley and colleagues, older adults were randomized to 3 months of cycling either with or without a virtual reality display (Anderson-Hanley et al., 2012). Participants in the intervention group (the ‘cybercyclists’) experienced 3D tours and competed with a ‘ghost’ rider that rode at the pace of their last best ride; in month 3, they were instructed to outpace on-screen riders. Both groups performed exercise at the same frequency, intensity and duration, but cybercyclists improved or maintained their performance on executive functioning tasks when the control cyclists showed no change or declines. These findings may suggest synergistic effects of mental and physical activity, or they may be due primarily to the unique mental stimulation of virtual reality.

**Neuroimaging in Physical Activity Research**

In the past decade researchers have begun using various neuroimaging modalities to study the underlying changes in the brain that occur with exercise training; the ultimate
goal is to show that these changes mediate the relationship between exercise and improved cognitive function (or reduced dementia risk). Structural magnetic resonance imaging (MRI) studies have measured changes in gray matter volume, white matter volume, and white matter integrity. Functional MRI (fMRI) studies have focused on changes in task-related and resting-state brain activity. Due to their direct relevance to the current proposal, fMRI studies that have investigated task-related brain activity as a function of exercise training or fitness are summarized below. Structural studies and fMRI studies focused on resting-state brain activity are also discussed briefly.

**Functional Neuroimaging Studies.** To preface the fMRI discussion, functional changes in the brain can be measured indirectly via tissue perfusion, blood volume, or blood oxygenation levels. The dominant fMRI measure is the latter, measured as the blood-oxygen-level-dependent (BOLD) contrast. The BOLD signal reflects a net decrease in deoxygenated blood in active brain regions. Deoxygenated haemoglobin has different magnetic properties than oxygenated haemoglobin, and therefore when a rush of oxygenated blood arrives at an active brain area, the altered (greater) ratio of oxygenated:deoxygenated haemoglobin is detected as the BOLD signal (Attwell & Iadecola, 2002).

Most exercise-fMRI studies have used executive functioning or memory tasks inside the scanner. Of the executive functioning studies, some have reported increases in task-related brain regions with exercise training/higher fitness (Liu-Ambrose et al., 2012; Prakash et al., 2011; Rosano et al., 2010) and some have reported decreases (Voelcker-Rehage, Godde, & Staudinger, 2010, 2011). One study reported both increases and decreases in different areas with training (Colcombe et al., 2004). In memory studies, most researchers report increases in brain activity with exercise training (Holzschneider,
Wolbers, Roder, & Hotting, 2012; Nagamatsu, Handy, Hsu, Voss, & Liu-Ambrose, 2012; Pereira et al., 2007; Smith et al., 2011), although in one study resistance but not aerobic training improved cognitive performance and increased brain activity (Nagamatsu et al., 2012), and in another fitness was related to increased brain activation during spatial memory performance, but only when participants also received spatial training (Holzschneider et al., 2012). Additionally, a cross-sectional positron emission tomography (PET) study found less brain activation during the learning and recall of word pairs in older men with a history of participation in endurance activity (Hollmann, Struder, Tagarakis, & King, 2007). These conflicting findings are hard to explain, especially if they are not mapped to improvements or decrements in cognitive performance. In general, authors that find increases in activity explain that fit older adults have an increased ability to engage task-relevant brain areas, whereas authors that find decreases claim that fit older adults are more efficient in their brain processing and require less compensation (i.e., their brains work more like young brains). Voelcker-Rehage and colleagues explain that both increases and decreases may reflect positive exercise-induced changes in brain function, and that differential findings may be due to differences in cognitive load, amount of practice in completing the task, and sample characteristics, as well as participants’ use of different cognitive strategies (Voelcker-Rehage & Niemann, 2013).

Researchers have also used fMRI to look at changes in the resting-state functional connectivity (i.e., temporal synchronicity) between different brain regions. In particular, Voss and colleagues found cross sectional evidence that higher fitness is associated with increased connectivity in the default mode network (Voss et al., 2010a). In a later
randomized controlled trial, Voss et al found exercise-induced improvements in both
default mode and frontal executive network connectivity at rest (Voss et al., 2010b). In
both studies, increased connectivity was linked with improved cognitive performance
(Voss et al., 2010a; Voss et al., 2010b).

**Other Neuroimaging Modalities.** Many studies have used structural MRI to
evaluate changes in total brain volume or regional gray matter volume with exercise
training or differences with high levels of fitness (Colcombe et al., 2003; Colcombe et al.,
2006; Erickson et al., 2009; Erickson et al., 2011; Ruscheweyh, 2011; Yuki et al., 2012).
These studies, as a whole, have complemented the fMRI literature in finding that exercise
seems to delay or reverse age-related shrinkage in frontal and temporal areas (Voelcker-
Rehage & Niemann, 2013). Although observed changes in brain volume do not always
correlate with or predict improved cognitive performance (and thus their significance
remains unclear), multiple studies have shown an association between increased
hippocampal volume and improved spatial memory performance (Erickson et al., 2009;
Erickson et al., 2011).

Other structural studies have focused on changes in white matter (which consists
mostly of myelinated axons). Most studies show no relationship between physical
activity and white matter volume or white matter integrity measured as lesions or
microintensities (abnormalities in white matter signals likely resulting from
demyelination, trauma, inflammation or other insults) (Park & Reuter-Lorenz, 2009;
Voelcker-Rehage & Niemann, 2013). Alternatively, multiple studies have found an
association between fitness and white matter integrity measured as fractional anisotropy
PET scanning has not yet been used to measure amyloid plaque buildup in relation to fitness (Johnson et al., 2013), which could potentially be useful in studying the effects of exercise on AD risk. PET could also be used to look at relevant changes in neurotransmission (e.g., dopamine, serotonin) with exercise training (Boecker, 2011). To my knowledge, no studies have used newer modalities such as arterial spin labeling (to determine changes in brain perfusion) or proton magnetic resonance spectroscopy (to look at changes in brain metabolites) in any cross sectional or longitudinal exercise studies.

**Conclusions.** In summary, the benefits of exercise for cognitive function in both healthy and cognitively impaired older adults have been repeatedly demonstrated. Many domains of cognitive function have been tested in exercise trials (e.g., memory, reaction time, attention), but the most robust effects have been found on executive functioning tasks (Colcombe & Kramer, 2003). Some researchers believe that this ‘selective effect’ may be even more specific to executive functioning tasks that are timed and especially demanding (Smiley-Oyen, Lowry, Francois, Kohut, & Ekkekakis, 2008). In many studies, the benefits have been larger in women (Baker et al., 2010b; Colcombe & Kramer, 2003). The majority of exercise trials have focused on aerobic exercise, perhaps due to the predominance of the cardiovascular fitness hypothesis, although recent studies have begun to study the cognitive benefits of resistance training (Cassilhas, 2007; Liu-Ambrose & Donaldson, 2008; Liu-Ambrose et al., 2012) and Tai Chi Chuan (Chang, Nien, Tsai, & Etnier, 2010).

Importantly, many studies are now attempting to link behavioral improvements in cognitive performance with underlying changes in the brain. According to a 2013 review
paper (Voelcker-Rehage & Niemann, 2013), a total of 12 studies (6 interventions) have used fMRI to investigate the relationship between exercise/fitness and brain function in adults; 9 of these studies (5 interventions) have focused specifically on older adults. Although the quality of neuroimaging studies varies (e.g., cross-sectional versus intervention, self-reported physical activity versus fitness measured via VO\textsubscript{2}max) and many fail to show a link between brain level changes and behavioral improvement, the majority of the ‘exercise cognitive-neuroscience’ research has provided exciting preliminary evidence that fitness may be neuroprotective, and that exercise training can induce adaptive changes in the brain over even short periods of time.

**Mediators and Moderators of the Exercise-Cognition Relationship**

Neuroimaging studies are mechanistic in that they attempt to explain what is happening in the brain at the systems level with exercise training, but they do not (for the most part) provide direct insight into cellular and molecular changes responsible for cognitive improvement. The biological mechanisms linking exercise and cognition are complex and poorly understood, but some highly plausible key players have been identified, both centrally and in the periphery. Although some studies suggest that exercise has a direct effect on AD pathology (e.g., reduced amyloid deposition in cortex) (Rolland, 2008), most mechanistic discussions focus on enhanced neuroplasticity and lower cardiovascular and metabolic risk factors with exercise. Studies have also provided insight into moderators of the exercise-cognition relationship (i.e., variables that predict which individuals may benefit most from exercise training).

At the cellular level, exercise has been shown to alter cytoarchitecture in the hippocampus, particularly in the dentate gyrus; these changes include increases in
dendritic length, dendritic complexity, and spine density. With these structural changes there are exercise-induced increases in synaptic proteins, glutamate receptors, and growth factors, all which promote synaptic plasticity, and, therefore, learning. In addition to priming pre-established neurons for learning, hippocampus neurogenesis is one of the most replicated cellular-level changes found in exercise studies. Although the behavioral significance of new neurons is unclear, they do become functionally integrated in the hippocampus, and have been linked with improved learning and memory. Increases in synaptic plasticity and neurogenesis come with increased energy demands, and therefore exercise also leads to a widespread growth of blood vessels for the delivery of oxygen and nutrients (Cotman, Berchtold, & Christie, 2007).

Three molecules thought to be highly responsible for exercise-induced neuroplasticity are brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1) and vascular endothelial-derived growth factor (VEGF). Upregulation of BDNF and IGF-1 in the hippocampus is thought to be key to enhanced hippocampal-dependent learning with exercise. Both of these growth factors also appear to have anti-depressant effects, which may overlap with or partially explain their effects on cognition. Peripheral increases in IGF-1 and VEGF are directly linked with exercise-induced neurogenesis and angiogenesis (Cotman et al., 2007). Although these molecules are clearly involved, the mechanisms of these mechanisms (i.e., the downstream effects) are largely unknown.

In the discussion of mediators linking exercise and cognition, it is important to stress that what is good for the body is also good for the brain. Many risk factors for cardiovascular disease and diabetes are also risk factors for dementia, especially
hypertension and glucose intolerance (Cotman et al., 2007; Rolland, 2008). Most peripheral risk factors that affect cognitive function involve systemic inflammation; Cotman and colleagues suggest that reducing peripheral inflammation is another means by which exercise increases the levels of key growth factors (as inflammation inhibits their function) (Cotman et al., 2007). There is also a direct effect of vascular health on risk of cognitive decline and dementia. Hypertension is one of the greatest risk factors for white matter damage, which has been associated with decrements in executive functioning and memory (Buckner, 2004). Lange-Asschenfeldt and Kodja advocate the concept of using exercise to build ‘vascular reserve’ to offset the vascular oxidative stress and reduced cerebral blood flow caused by early AD pathology (Lange-Asschenfeldt & Kojda, 2008).

Many human studies testing the relationship between physical activity/exercise and cognitive function have been designed under the premise that gains in cardiovascular fitness are necessary for these cellular, molecular and systems level changes to occur (and therefore, for cognition to improve). In 2006, Etnier and colleagues conducted a meta-regression of 37 human studies to specifically test this hypothesis (Etnier, Nowell, Landers, & Sibley, 2006). Although they found an average effect size of 0.34 for improvements in cognitive performance with fitness/exercise training, there was no evidence from cross-sectional, posttest comparison or pre-post comparison studies to support the cardiovascular fitness hypothesis. In fact, pre-post studies actually showed that larger gains in fitness were predictive of smaller improvements in cognitive performance. Despite these findings, Etnier et al acknowledge that improvements in fitness may still be necessary for cognitive improvement, but that it may be the first step
in a cascade of physiological events and may simply not be a sensitive enough measure of mediation. It may also be the case that psychological or physiological events unrelated to aerobic fitness are the true mediators of the exercise-cognition relationship in humans.

Gender and genotype are often discussed as important moderators of the physical activity-cognition relationship. Many studies have found greater neuroprotective effects in women (Colcombe & Kramer, 2003), possibly due to an interaction between the cognitive-enhancing effects of estrogens and physical activity (Erickson et al., 2007; Rolland, 2008). Alternatively, women may not benefit more than men, but smaller samples of men may have precluded the detection of cognitive improvements. There is also debate over the effect of ApoE genotype on response to exercise training; some studies show a greater effect in individuals with risky genotypes (i.e., ApoE-ε4 carriers) (Etnier et al., 2007) and other show a lesser effect (Kramer, Erickson, & Colcombe, 2006; Rolland, 2008).

Conclusions. Research suggests that exercise can improve cognitive function and/or lower the risk of cognitive decline and dementia via brain-specific (e.g., enhanced neuroplasticity) and general peripheral (e.g., reduced inflammation, increased insulin sensitivity) mechanisms. Exercise is unique from many other prevention or treatment options in this sense (with the exception of dietary changes). Interestingly, animal studies have largely used hippocampal-mediated learning and memory tasks, whereas human studies have predominately focused on prefrontal cortex-mediated executive functioning; thus, it is unclear whether mechanisms established in animal work explain executive functioning improvements in humans. From human studies we have learned that cardiovascular fitness may not be necessary for cognitive improvement (Etnier et al.,
2006), and that gender and ApoE genotype appear to influence the effectiveness of physical activity in preserving brain and cognitive function.

**Cognitive Reserve (CR) Theory**

The last section of this literature review discusses the theoretical basis of the current proposal. As mentioned previously, CR theory was originally developed to explain the discordance between clinical symptoms of AD and severity of AD pathology upon autopsy (i.e., amyloid plaques, neurofibrillary tangles, widespread atrophy). The theory posits that engaging in mental and physical activities may protect against cognitive decline in the face of brain insult (e.g., normal aging, neurodegenerative conditions, traumatic brain injury). When a healthy individual ‘builds’ CR, the neural processing underlying his or her cognitive performance becomes more efficient, more flexible and/or more capable of recruiting necessary resources. The idea is that neural networks or circuits that are functioning in this manner are more difficult to disrupt. Importantly, it is believed that individuals can continue to build their CR throughout life; it is never too late to start.

This dissertation was designed to test CR theory from an exercise science standpoint; that is, I investigated whether the adoption of a physically active lifestyle could increase CR in the aged brain. To do this, I based my methodology on the previous work of Stern and colleagues at Columbia University. Stern is a leading proponent of CR theory, and his work has focused particularly on the prevention of AD. In this section I explain the systematic approach Stern and colleagues have developed and utilized for exploring the neural basis of CR, and cite relevant studies using this approach.
Stern suggests that the mechanisms of CR may be divided into two subcomponents of neural processing in the brain: neural reserve and neural compensation. Neural reserve refers to inter-individual variation in the efficiency, capacity or flexibility of brain networks subserving cognitive functions in the healthy brain. A brain that is more efficient (i.e., requires fewer neural resources), capable (i.e., can recruit more neural resources) and/or flexible (i.e., can use multiple networks to accomplish the same task) is thought to be less susceptible to disruption when met with a challenge. Alternatively, neural compensation refers to the ability to use alternative brain networks when original networks are damaged (Stern, 2009). Neural reserve and neural compensation are considered active models for maintaining cognitive function, as opposed to the related passive model of brain reserve. Brain reserve simply implies that pathology will translate to behavioral impairment when a critical atrophy threshold is reached (i.e., bigger brains are better) without considering neural processing (Stern, 2009). Although this terminology is not universal (for example, some researchers use ‘neurological brain reserve’ rather than ‘brain reserve’, and ‘behavioral brain reserve’ rather than ‘cognitive reserve’ (Valenzuela & Sachdev, 2006), I use Stern’s terminology and definitions throughout this review.

**Testing CR Theory using fMRI.** The major difference between neuroimaging studies testing the neural basis of CR and more general studies of cognition in aging is the focus on individual variability and, most often, how that variability relates to a proxy variable of mental activity (e.g., years of education, innate IQ, level of occupational attainment) (Stern, 2009). The assumption is that differences in task-related brain activation provide insight into the neural implementation of CR. Differences in patterns
of task-related activation can be assessed across groups of individuals (e.g., young versus old) or within a group of individuals as a function of some proxy of mental activity. Neural network efficiency and capacity are more straightforward to study using fMRI than neural network flexibility or compensation (Stern, 2009), and thus Stern’s approach focuses on the former. It should be noted that although Stern and colleagues use verbal and non-verbal working memory tasks to test CR theory, CR likely mediates advantageous neural processing during the performance of a variety of cognitive tasks, and may do so via a non-task-specific assistive network (Stern, 2009).

When performing a relatively easy cognitive task, individuals with greater CR may be more efficient; in terms of the BOLD signal, this may be reflected in lower activation. Importantly, because the task is not challenging, performance will likely be consistent across individuals regardless of brain efficiency. When using a within-subjects approach, efficiency can also be expressed by lesser increases in activation (within the same network) when switching from low to higher-demand cognitive tasks. Alternatively, in what seems paradoxical, individuals with more CR may show greater increases during this switch. This may occur because individuals with greater CR may have a greater capacity to recruit neural resources within the same network when performing a challenging cognitive task; this may be reflected as a large increase in BOLD signal activation in the task-related network, and better behavioral performance. Two studies discussed below suggest that age may determine which of these neural reserve forms CR will take (i.e., more CR in the older adult brain may present differently than it would in the young adult brain (Scarmeas et al., 2003; Stern et al., 2005). With increasing cognitive demands, older adults with more CR may also show activation in different or
additional brain regions; this would be evidence of neural compensation rather than neural reserve.

Using this theoretical framework, Habeck et al. found that healthy young adults with higher IQs showed greater neural efficiency (identified as a smaller increase in network activation with increasing task difficulty) during the retention phase of a verbal memory task performance (Habeck et al., 2005). Greater efficiency also correlated with lower reaction time. Another study by Habeck et al. showed that young adults with higher IQs displayed greater neural efficiency during the encoding and recognition phase of a shape recognition task (Habeck et al., 2003). In a study comparing the brain activation patterns of young and older adults (based on the assumption that young adult neural processing is preferable), Zarahn et al. found that both groups used the same networks during the encoding and recognition phases of a verbal memory task; follow up analyses found that the younger adults were more efficient during encoding but not recognition (Zarahn et al., 2007). Young and older adult networks differed, however, during the retention phase. Follow up analyses determined that the differential network recruitment used by older adults was actually associated with poorer performance; a later study confirmed that loss of gray matter density in a key region of the original network used by young adults (left precentral gyrus) was associated with use of the secondary network (i.e., older adults may have been unsuccessfully trying to compensate for age-related atrophy) (Steffener, Habeck, & Stern, 2012). In a similar study of young and old adults completing a shape memory task, young adults showed greater task-related neural capacity, rather than efficiency, during the probe phase (i.e., young adults performed better and showed greater task-related network activation) (Holtzer et al., 2009).
Other studies have compared not just young and older adults, but also young and older adults with varying levels of mental activity engagement. In a 2003 PET study, Scarmeas et al found that changes in brain activation with increasing task demand (more shapes to remember) correlated with a composite variable of education and IQ measures (Scarmeas et al., 2003). The major finding from this study was that young adults with high education/IQ showed relatively large increases in activity in some brain regions where older adults with high education/IQ showed relatively small increases; this suggests that CR may present differently in the face of age-related neural changes. A second PET study using the same shape memory task and composite variable found similar results when using different a different analytic approach (looking at covariance networks rather than separate brain regions); older adults with high education/IQ showed an opposite pattern of activation from young adults with high education/IQ (Stern et al., 2005).

**Conclusions.** CR theory is exciting because it suggests that, through our lifestyle choices, we have a degree of control over how our brain’s age and whether or not our cognitive function is preserved. Stern and colleagues have shown that differential brain activation as a function IQ (a proxy variable of mental activity) can be observed even in young adults (Habeck et al., 2003; Habeck et al., 2005). Using the young brain as the ‘gold standard’, they have also found differences in efficiency and capacity in the young versus older adult brain during memory task performance, as well as the use of compensatory brain networks in older adults (Holtzer et al., 2009; Zarahn et al., 2007). Lastly, they have established that CR may manifest differently in the young versus older adult brain; this finding suggests that although the task-related networks used in the
young, high-CR brain is ideal, reliance solely on these networks might not be attainable even in the most advantageously functioning older adult brain. For intervention purposes, the goal may therefore not be to make an old brain look young, but to make an old brain look like a healthier old brain.

Of critical importance to the current project, and perhaps the driving factor in its development, no studies have used Stern’s systematic approach to testing CR theory using a proxy variable of physical activity rather than mental activity. Further, although Stern and colleagues suggest that it is never too late to start building CR, they have not demonstrated this phenomenon in intervention work with older adults. These gaps in the literature raise a number of questions: Does physical activity or exercise participation build CR? If so, can significant increases in CR be observed after only a few months of training? This seems plausible, as other fMRI studies with older adults have shown changes in brain activity after relatively short periods of exercise training. If CR can be built rapidly with exercise training, do these changes lead to immediate improvements in cognitive performance? Or will the behavioral benefits of exercise-induced CR only be observable later in life? Although randomized exercise trials with long follow-up periods would clearly be an ideal approach to answer these questions, much can still be learned from trials with only immediate follow up; namely, these studies can show us whether a relatively short period of exercise training can lead to increases in CR in the aged brain.
Chapter 3: Methods

Overview of the Parent Study: WeWalk

The current studies were performed in collaboration with an on-going study in the exercise science department led by Dr. Xuewen Wang. For the WeWalk study, older women (n=72) are randomized to either a higher (14 kcal/kg body weight, weekly) or lower-dose (8 kcal/kg body weight, weekly) 16-week aerobic exercise program. Supervised exercise is performed at a moderate intensity (60-65% VO$_2$ max), 3 d/wk, and primarily consists of walking and jogging on an inclined motor-driven treadmill. The difference between the higher and lower-dose programs is one of session duration; women in the higher dose program walk, on average, 55-60 minutes per session, while women in the lower dose program walk, on average 30-35 minutes per session. Prior to and at the completion of the program, participants undergo a graded exercise test to determine maximum oxygen consumption (VO$_2$ max).

Study 1

Purpose

This study addressed Aim 1: To determine whether participation in an exercise training program builds CR, evidenced by greater efficiency in a task-related brain network.
Hypotheses

1.1. Relative to baseline, it was hypothesized that there would be a smaller difference in task-related neural network activation during low versus high-demand working memory trials after completion of the 16-week exercise program. Although the task-related network was expected to encompass a wide range of brain areas, changes in task-related activation with exercise training were expected in premotor, parietal, inferior frontal and middle frontal areas (Zarahn et al., 2007).

1.2. It was hypothesized that greater improvement in fitness would correlate with greater improvement in efficiency in the working memory network.

1.3. It was hypothesized that greater efficiency in the working memory network would correlate with better performance (i.e. reaction time slope).

Design

The experiment was a quasi-experimental pilot study (pre-post, no control group).

Participants

A sub-set of healthy older women participating in *WeWalk* (n=17) participated in this study. After meeting the eligibility criteria for *WeWalk* (e.g., age 60-75 yrs, sedentary for previous 3 mo), additional inclusion criteria for my study were: 1) visual acuity of at least 20/40 (with or without contacts) and 2) right-handedness. Additional or overlapping exclusion criteria were: 1) mild cognitive impairment or dementia, 2), history of alcohol abuse, stroke, major depressive disorder or another psychiatric disorder, or traumatic brain injury, and 3) contraindications for MRI scanning, which included
implanted medical devices, joint replacements, and history of certain medical conditions or claustrophobia.

Recruitment

At the first of six *WeWalk* baseline sessions (session B1), I was given the opportunity to talk to *WeWalk* participants about additional participation in my study (session B1 is held approximately 4-5 weeks before *WeWalk* baseline testing is complete and exercise training begins). Individuals who indicated an interest in additionally participating in my study were contacted by phone, and baseline session 1 was scheduled for those still interested.

Procedures

**Baseline Session 1.** Prior to beginning the 16-week exercise program, participants came to the McCausland Center for Brain Imaging (MCBI) at Palmetto Richland Hospital for their first baseline session (120 min). Participants were asked not to participate in any moderate or vigorous physical activity 48 hours prior to their arrival to avoid any acute effects of exercise on cognitive performance. Upon arrival, participants reviewed and signed a consent form approved by the USC IRB. I summarized and orally restated the major sections of the consent form and gave participants the opportunity to ask questions. Consenting participants completed a series of computerized, touch-screen cognitive tasks to assess performance in different cognitive domains. Participants also completed a MRI screening document, health history form, and IQ test at this time, and were scheduled for their MRI session. Lastly, they were given a Lifetime Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) to complete at home and return at their upcoming MRI session. Of note,
participants completed 5 questions from the Profile of Mood States (McNair, Lorr, & Droppleman, 1992) relating to nervousness/anxiety prior to all cognitive testing and MRI scanning to verify that pre-post changes were not the result of greater familiarity and lower stress at post-testing.

**Baseline Session 2.** Participants returned to the MCBI for their second baseline session (90 min total) prior to beginning their exercise training program. Once again, participants were asked not to participate in any moderate or vigorous physical activity 48 hours prior to their MRI scanning appointment. Prior to scanning, contraindications for MRI scanning were discussed again, informed consent was obtained, and participants changed into MRI safe attire (if necessary). Participants also practiced the task on a computer monitor outside of the scanner until they were comfortable (usually 5-10 minutes). For each participant, we acquired a structural image and functional images during the performance of a working memory task. Participants underwent 55 total minutes of MRI scanning.

**Follow Up Sessions 1 & 2.** Within the final week or up to 1 week after the completion of the 16-week exercise program, participants came to the MCBI to repeat the computerized cognitive battery performed at Baseline Session 1 (60 min) and to complete a follow up MRI scan (90 min). Cognitive testing and MRI scanning procedures at follow up were the same as at baseline. Participants had the option to complete both follow up sessions on the same day to minimize travel time and scheduling conflicts.

**Compensation.** Participants were given $20 at the completion of each session, for a total of $80 if they complete the study in its entirety. At the completion of the
follow-up scanning session, each participant also received a CD with a picture of her brain (i.e., her structural MRI scan).

**Measures**

The following are assessed as part of *WeWalk* screening and data collection:

**Sociodemographics.** Participants provide their date of birth, race, highest grade/level of school completed, total yearly household/family income, work/retirement status, and marital/relationship status.

**Medical History.** Participants provide general self-rated health information, as well as information regarding specific health conditions past and present (e.g., hypertension, heart conditions, diabetes). Participants also indicate whether or not they smoke and what medications they are currently taking.

**Cognitive Impairment.** The Mini Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) is used to screen for dementia. Participants scoring lower than 24 are excluded from participation in *WeWalk*.

**Depression.** The Center for Epidemiologic Studies Depression Scale (Radloff, 1977) is used to screen for depression. Participants scoring higher than 16 are excluded from participation in *WeWalk*.

**Aerobic Fitness.** A graded exercise test (modified Astrand-Saltin protocol (Hawkins, Raven, Snell, Stray-Gundersen, & Levine, 2007; Levine & Stray-Gundersen, 1997) determines fitness, measured as maximum oxygen consumption (VO$_2$max). Before starting the test, a trained exercise physiologist measures heart rate and blood pressure and conducts a standard 12-lead ECG; ECG, heart rate, blood pressure, rating of perceived exertion, and treadmill speed and grade are recorded at each stage of the
protocol. Participants perform the test at a constant, self-selected walking speed. The treadmill grade is increased 2% every 2 minutes until volitional exhaustion (usually occurring 8-12 minutes after the start of the test). The test may be terminated early by study staff if exercise blood pressure exceeds 250/115 mmHg or if abnormal ECG tracings are observed. All tests are performed under the supervision of the WeWalk medical director.

The following were additionally assessed in the current study:

**Demographics/Health History.** Three demographic/health history questions not addressed as part of WeWalk were asked: 1) ‘Have you ever taken hormone replacement therapy? If so, for how long?’, 2) ‘Have you ever experienced a traumatic brain injury?’, and 3) ‘Have you ever had an alcohol or other drug addiction?’.

**MRI Safety.** The MCBI’s MRI Participant Screening Document was used to ensure that all participants could safely undergo MRI scanning. The document asks about metal in or on the body, past surgical procedures, relevant medical conditions, and claustrophobia.

**Handedness.** An abbreviated version of the Edinburgh Handedness Inventory determined handedness (Oldfield, 1971; Veale, 2013).

**History of Leisure Activity.** A modified version of the Lifetime Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) assessed complex mental activity throughout the lifespan. This questionnaire assesses educational, occupational and leisure activities in young adulthood (13-30y), midlife (30-60y) and late life (60y+).

**Intelligence.** The Wechsler Abbreviated Scale of Intelligence, two-subtest form was used to obtain a brief measure of intelligence (WASI FSIQ-2) (Psychological
This abbreviated measure can be issued in 15 minutes, and includes a vocabulary test and a matrix-reasoning test. The vocabulary test assesses word knowledge, verbal concept formation, and fund of knowledge; as responses are subjective, I transcribed the participants’ responses verbatim and Dr. Wilcox later assisted in scoring. The matrix-reasoning test assesses visual information processing and abstract reasoning skills. For this test, participants select the missing portion of a pattern from five possible choices (responses are objective [correct or incorrect]). A combined score from the two tests was used as the measure of IQ.

**Cognitive Function.** The Cambridge Neuropsychological Test Automated Battery (CANTAB®) is a series of computerized, touch-screen tasks used to assess performance in different cognitive domains. Performance in the domains tested in this study have been shown to predict rates of cognitive decline (Blacker et al., 2007; Collie, Maruff, & Currie, 2002; De Jager, Blackwell, Budge, & Sahakian, 2005; De Jager & Budge, 2005) and/or have been shown to improve with exercise training (Colcombe & Kramer, 2003). Prior to completing the chosen battery, the Motor Screening Task was used to introduce the participant to the touch screen; the task screens for visual, movement or comprehension difficulties and takes approximately 2 minutes.

**Sustained Attention.** The Rapid Visual Information Processing task is a measure of sustained attention and general performance. During this task, digits from 2 to 9 appear in random order at the rate of 100 digits per minute; participants must detect sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). Outcome measures include hits, misses, false alarms and rejections. The task takes 7 minutes.
**Visuospatial learning.** The Paired Associates Learning task is a challenging test of visual memory and new learning. During this task, boxes around the perimeter of the screen are opened in random order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, and the participant must touch the box where each pattern was originally seen. Outcome measures include number of errors made, number of trials required to locate the pattern(s) correctly, memory scores and stages completed. The task takes about 10 minutes.

**Working memory.** Spatial Span was used to assess working memory capacity. For this task, a series of boxes (starting at two and increasing to nine) change color in sequence and the participant must touch the boxes in the same order that they changed. Outcome measures include span length achieved and errors. The task takes about 5 minutes.

**Verbal memory.** The Verbal Recognition Memory task tested free recall and recognition memory. To complete this task, participants are shown a list of 12 words and asked to: produce as many words as possible immediately after presentation, recognize the original words from a list of 24 (12 original words, 12 distractors), recognize the original word list from another list of 24 following a 20 minute delay. Outcome measures include correct and incorrect responses. This task takes about 7 minutes.

**Cognitive Reserve (CR).** A delayed-match-to-sample working memory task was used in the scanner to assess CR. During this task, participants were presented with one, three, or six capital letters for three seconds, followed by a one-letter recognition probe (a lower-case letter that was or was not in the previous set) seven seconds later. Subjects were asked to respond ‘yes’ or ‘no’ with a left or right button press to indicate whether or
not the probe letter was part of the previous set. This letter memory task (Habeck et al., 2005; Steffener et al., 2012; Stern et al., 2008; Zarahn et al., 2007), as well as similar working memory tasks using abstract shapes (Habeck et al., 2003; Holtzer et al., 2009; Scarmeas et al., 2003; Stern et al., 2005; Stern et al., 2008; Stern et al., 2003), has been utilized in multiple MRI investigations of CR mechanisms because the internal manipulation of difficulty (i.e., changes in memory load) is ideal for studying how neural processing changes in the face of a challenge. Behaviorally, reaction time slope with increasing set size is an indicator of working memory scanning speed (Stern, 2009).

**Statistical Analyses**

MRI data were analyzed using SPM8, a MATLAB based software package specifically designed to analyze brain imaging data (www.fil.ion.ucl.ac.uk/spm/). All data were preprocessed using standard SPM protocols (realignment, coregistration, normalization and smoothing). Brain areas involved in the performance of each task condition (i.e., 6-, 3-, and 1-letter trials) were identified using baseline data. Next we modeled the following events in a first-level analysis: high-demand trials (6-letter trials) and low-demand trials (1-letter trials). For each individual participant we calculated a statistical parametric map that subtracted brain activation during low-demand trial performance from activation during high-demand trial performance to identify the areas where the BOLD signal changed with increasing cognitive demand. These first-level analyses were conducted on both baseline and post-exercise scans, and focused specifically on activity during the retention phase of each trial (rather than the encoding or recognition phase). Next we created models for each individual participant that compared changes in brain activation (high-demand minus low-demand) at post scan and
pre scan (post minus pre). These maps were entered into a second-level random-effects (group) analysis, and parameter estimates for changes in BOLD activation with exercise training were extracted.

For reaction time analyses, reaction times corresponding with response errors were removed, and means and standard deviations for 1-, 3-, and 6-letter sets (across all 3 runs) were calculated. Reaction times $\geq 2$ standard deviations from their respective means were then also removed. Reaction time slope with increasing set size (1 to 3 to 6 letters) was calculated using the 1-, 3- and 6- letter mean reaction time values for both baseline and post-exercise scanning data.

Basic descriptive statistics were run in SAS, and included frequencies and means of key variables (age, health status, IQ, lifetime experience, baseline fitness, group randomization). PROC UNIVARIATE was used to test the distribution and skewness of these variables. Residualized changes scores were created to determine change in fitness and change in reaction time slope and used in place of simple change scores in all analyses.

**Hypothesis 1.1.** Based on my a priori hypothesis, a one-tailed paired/repeated measures t-test determined whether the difference in task-related network activation during low versus high-demand trials was smaller after exercise program completion. Although the sample size was too small to control for covariates, the data was divided using medians splits to look for trends relating the observed changes in brain activation with the following variables of interest: age, IQ, lifetime experiences, randomization group, family history of dementia, and baseline fitness.
**Hypothesis 1.2.** Pearson’s correlation coefficient determined whether change in aerobic fitness was associated with change in neural network efficiency, measured as the difference in task-related network activation during low versus high-demand trials. Pearson’s correlations were also run between neural network efficiency and four other variables (age, health status, lifetime experience score, and baseline fitness) to verify that the observed correlation between change in aerobic fitness and change in efficiency was unique.

**Hypothesis 1.3.** Pearson’s correlation coefficient determined whether change in neural network efficiency was associated with change in task performance, measured as a change in mean reaction time slope (between low and high-demand trials).

**Power.** This project was a pilot study and was expected to be underpowered, however power calculations were run using G*Power 3.1 to determine the effect size required with the originally planned sample size (n=15, pre-post). In examining pre-post differences in task-related network activation, our repeated measures, one-tailed t-test had 80% power to detect an effect size of approximately 0.68 ($\alpha=.05$). Our study had 80% power to detect correlations of .60 ($\alpha=.05$) between change in neural network efficiency and both change in fitness and reaction time. Using a proxy variable of mental activity (an index of education and IQ) rather than physical activity, but a similar working memory task, Stern et al found a correlation of -.50 between level of mental activity and CR in older adults (n=17)(Stern et al., 2005). Fitness was expected to be equally or more highly correlated with CR. Of note, it was realistic to expect fitness improvements over the 4-month study period; in a similar exercise trial, older adults who participated in 6 months of aerobic exercise (40-45 min/3d/wk) improved their VO$_2$max 10.2% (compared
to a stretching and toning control group that improved only 2.9%) (Colcombe et al., 2004).

Study 2

Purpose

This study addressed Aim 2: To determine whether participation in an exercise training program improves cognitive performance.

Hypotheses

2.1. It was hypothesized that participation in a 16-week exercise program would improve sustained attention, visuospatial learning, spatial working memory, verbal free recall, and verbal recognition memory (immediate and delayed), as compared to no exercise.

2.2. It was hypothesized that greater improvement in cognitive performance would correlate with greater improvement in fitness.

Design

The proposed research was a quasi-experimental pilot study (non-randomized, controlled).

Participants

The sub-sample of women from WeWalk who participated in Study 1 (n=17) also participated in Study 2. Additional WeWalk participants were part of Study 2, only (i.e., no MRI; n=5). Study 2 also included a non-randomized, no exercise control group (n=19). Inclusion/exclusion criteria for the control group were the same as the for the WeWalk study with one exception- control group participants were not excluded for
having a physical limitation that would preclude exercise training. A total of 41 women participated in Study 2.

Recruitment

Recruitment efforts for participants in the experimental (exercise group) were described in Study 1. Additional women from the community were recruited through a newspaper advertisement and word of mouth to serve as the non-exercise control group. Recruitment efforts for the control group advertised a study relating to memory and thinking skills. Individuals interested in the memory and thinking study also completed an initial screening with the WeWalk study coordinator.

Procedures

For intervention group data collection, procedures for Study 2 were identical to Study 1, except that the additional WeWalk participants recruited for Study 2, only, did not undergo MRI scanning. Thus, these participants (n=5) partook in Baseline Session 1 and Follow-up Session 1, only.

For control group data collection, we followed near identical cognitive testing procedures, asking participants (n=19) to complete their two sessions approximately 16 weeks apart. Prior to their baseline session we mailed a packet of questionnaires (completed by the intervention group as part of WeWalk participation), which participants completed and brought with them to their baseline session. We conducted dementia screening using the MMSE at the baseline session. We measured height, weight and blood pressure at baseline, and weight and blood pressure again at post-testing. We asked control group participants not to begin a structured exercise program in the 16 weeks between sessions.
Compensation. Intervention participants in Study 2, only, and control group participants received $20 at the completion of each session, for a total of $40 if they completed the study in its entirety.

Measures

For the intervention (exercise) group, Study 2 measures were identical to those used in Study 1 except that the MRI safety questionnaire and CR MRI task were not administered. Additional measures collected with control participants were height, weight, and blood pressure. Height was measured with a Seca mobile stadiometer to the nearest quarter inch. Weight was measured with a Seca scale to the nearest tenth of a pound. Blood pressure was measured using an Omron Automatic Blood Pressure Monitor (Model HEM-780). We asked control group participants not to begin a structured exercise program in the 16 weeks between sessions.

Statistical Analyses

We performed analyses using SAS, version 9.3 (SAS Institute, Inc., Cary, NC). Basic descriptive statistics included frequencies and means of key variables. PROC UNIVARIATE tested the distribution and skewness of these variables. Chi-square and t-tests assessed differences between groups at baseline. We created residualized change scores for change variables (e.g., changes in fitness, cognitive performance) and used them instead of simple change scores in all ANOVA and correlation analyses.

Hypothesis 2.1. Repeated measures ANOVA determined whether performance on any of the cognitive tasks (rapid visual information processing [total hits], paired associates learning [total trials], spatial span [span length achieved], immediate verbal recall [number of correct responses]) improved with exercise training as compared to no
exercise. Separate paired t-tests verified the relationship between exercise training and change in performance on each cognitive task. Due to the small sample size, we also calculated effect sizes to assess the magnitude of change in cognitive performance within and between groups. We divided the exercise group by randomization assignment (high or low exercise group), and conducted an ANOVA to determine whether there were differential changes in cognitive performance based on exercise dose (high, low, no exercise [control]). The exercise group was also divided based on age, baseline fitness, IQ score, lifetime experience (median splits), and family history of AD (yes/no) to look for trends relating to changes in cognitive performance (paired t-tests).

**Hypothesis 2.2.** For each cognitive task, Pearson’s correlation determined whether change in aerobic fitness was associated with change in cognitive performance in intervention participants.

**Power.** This project was a pilot study and was expected to be underpowered, however power calculations were run using G*Power 3.1 to determine the effect size required with the originally planned sample size (n=40). In examining the effect of program participation on change in cognitive performance, our repeated measures ANOVA had 80% power to detect an effect size of approximately 0.39 ($\alpha=.05$). In the 2003 meta-analysis by Colcombe and Kramer, the effect size for exercise trials testing the same domain of cognitive function (executive function, memory) was 0.48 (Colcombe & Kramer, 2003). Our study had 80% power to detect correlations of .42 ($\alpha=.05$) between change in fitness and change in cognitive performance.
Chapter 4: Exercise and Cognitive Reserve:

An fMRI Investigation in Healthy Older Women¹

¹ Becofsky, K.M., Newman-Norlund, R., Wilcox, S., & Wang, X. To be submitted to Psychology and Aging
Abstract

Cognitive reserve theory suggests that physical activity may protect individuals from cognitive decline. At the brain level, cognitive reserve may manifest as neural network efficiency. Our purpose was to determine 1) whether participation in a 16-week walking program increased brain efficiency, and 2) whether change in fitness and cognitive performance correlated with increased brain efficiency. Twelve participants underwent fMRI scanning before and after exercise training. During scanning, participants completed the Sternberg delayed-match-to-sample letter task. Brain activation during the low-demand task condition was subtracted from brain activation during the high-demand condition. We expected this difference to become lesser with exercise training. Within our sample (100% female; mean age 63), the difference became greater in the following brain regions with exercise training: left inferior frontal gyrus, left cuneus, right rolandic operculum, left middle temporal gyrus, left postcentral gyrus, left superior med frontal, left superior frontal gyrus, right caudate, right inferior temporal gyrus (ps < 0.001). No task-related brain regions were utilized more efficiently after exercise training (ps > 0.001). These findings suggest that exercise-induced cognitive reserve may present as a greater ability to recruit neural resources, rather than greater brain efficiency, in this sample. As there were no significant correlations between change in task-related brain activation and change in performance (reaction time slope) with exercise training (r values < 0.49), these findings should be interpreted with caution.

Keywords: Walking, physical activity, brain health, dementia prevention
Exercise and Cognitive Reserve: An fMRI Investigation in Healthy Older Women

An estimated 5.2 million Americans will have dementia due to Alzheimer’s disease (AD) in 2014 (Alzheimer's Association, 2014). A projected 7.1 Americans will have the disease by 2025, and this number is expected to swell to 13.8-16 million by 2050 (Alzheimer's Association, 2014). Although AD is officially listed as the 6th leading cause of death in the US, a recent report suggests that AD-related deaths are vastly underreported (James et al., 2014). Although current pharmacological treatments (namely cholinesterase inhibitors, including donepezil, galantamine, and rivastigmine) may help with some cognitive and behavioral symptoms of AD, they cannot stop or reverse AD progression (U.S. Department of Health and Human Services, 2008).

Importantly, pathological changes in the brain may begin more than two decades before AD symptoms present (Alzheimer's Association, 2014), meaning it is already too late to prevent the onset of pathology in much of the aging baby boomer generation (i.e., individuals born between 1946 and 1964). Although the disease is already developing in many Americans aged 40+, it may still be possible to effectively intervene to prevent the dementia. Interventions aimed at building cognitive reserve may help prevent AD pathology from manifesting as dementia.

Cognitive reserve theory was developed to explain the discordance between severity of AD pathology upon autopsy (i.e., amyloid plaques, neurofibrillary tangles, widespread atrophy) and clinical symptoms of AD at death (Stern, 2009). The theory posits that certain exposures during life, namely mental stimulation, social engagement, and physical activity, may allow an individual to maintain his or her cognitive abilities in the face of advancing pathology by making the brain more efficient, more flexible and/or
more capable of recruiting necessary resources (Stern, 2006, 2009). Importantly, it is believed that individuals can continue to ‘build’ cognitive reserve throughout life— it is never too late to start (Scarmeas, Levy, Tang, Manly, & Stern, 2001). Thus, until scientists find ways to detect AD in asymptomatic individuals and intervene effectively, prevention efforts with cognitively intact middle-aged and older adults might focus on building cognitive reserve.

The current study used a systematic neuroimaging approach to investigate whether the adoption of a physically active lifestyle increases cognitive reserve in the aged brain. The approach, developed by Stern and colleagues (Stern, 2009), focuses on individual variability in task-related brain activity and, most often, how that variability relates to a proxy variable of mental activity (e.g., years of education, innate IQ) (Habeck et al., 2005; Steffener et al., 2012; Zarahn et al., 2007). The assumption is that differences in task-related activation provide insight into the neural implementation of cognitive reserve. Greater efficiency may be expressed as lesser increases in activation when switching from a low to higher-demand task condition with equivalent or superior performance. Alternatively, greater capacity to recruit neural resources may be reflected as larger increases and better performance. This study is the first to use this approach to test the contribution of physical activity, rather than mental activity, to building cognitive reserve, and the first to attempt to demonstrate the cognitive reserve phenomenon in physical activity intervention work with older adults.

In the current study, we hypothesized that 16 weeks of supervised exercise training would lead to greater brain efficiency in healthy older women. Our
emphasis on the efficiency mechanism rather than the capacity mechanism was based on previous research demonstrating the efficiency pathway (albeit in relation to mental activity) in older adult samples (Scarmeas et al., 2003; Stern et al., 2005). We hypothesized that greater improvement in fitness would correlate with greater gains in efficiency, and that greater gains in efficiency would correlate with greater improvements in performance, indicated by reaction time slope. Although the task-related network was expected to encompass a wide range of brain areas, changes in task-related activation with exercise training were expected in premotor, parietal, inferior frontal and middle frontal areas (Zarahn et al., 2007).

Methods

The current study used a quasi-experimental design (pre-post, no control group) to determine whether participation in an exercise training program builds cognitive reserve, evidenced by greater efficiency in a task-related brain network (measured using functional magnetic resonance imaging [fMRI]).

Participants

Participants are a sub-sample of women (n=12) participating in an on-going randomized exercise trial. The WeWalk study is investigating the effects of a chronic aerobic exercise program on energy expenditure compensation in older women. Healthy yet sedentary women (N=72) are randomized to either a higher (14 kcal/kg body weight, weekly) or lower-dose (8 kcal/kg body weight, weekly) 16-week exercise program. Supervised exercise is performed at a moderate intensity (60-65% VO_{2max}), 3 days per week, and primarily consists of walking and jogging on an inclined motor-driven treadmill. The difference between the higher and lower-dose programs is one of session
duration; women in the higher dose program walk, on average, 55-60 minutes per session, while women in the lower dose program walk, on average 30-35 minutes per session.

Women are recruited for the *WeWalk* study on a rolling basis via newspaper advertisements, flyers, university listservs, and university newsletters. Interested participants complete an initial phone screening with the study coordinator. To be eligible, women must be: 1) age 60-75 yrs, 2) body mass index (BMI) greater than 18 but less than 30 kg/m$^2$, 3) weight stable (±5%) during the previous 3 months, 4) underactive for the previous 3 months (<20 min, 3 times/week of resistance or endurance exercise), and 5) non-smoking for the past year. Exclusion criteria include: 1) self-reported significant cardiovascular disease (e.g., cardiomyopathy, myocardial infarction), 2) other self-reported medical conditions, including but not limited to metabolic disease (e.g., diabetes), chronic or recurrent respiratory conditions, active cancer, musculoskeletal disease interfering with exercise, or any serious medical condition that may affect adherence to the protocol or exercising safely, or be aggravated by exercise, 3) medications known to affect exercise performance or metabolism (e.g., hyperthyroid medication, β-blockers, stimulants), 3) excess caffeine use (>500mg/day), 4) any self-reported contraindications to exercise according to the American College of Sports Medicine criteria (American College of Sport Medicine, 2010).

Participants for the current sub-study were recruited in-person at the first of six *WeWalk* baseline sessions, held approximately 4-5 weeks before exercise training began. Because the current study involved cognitive testing and brain scanning, additional or overlapping exclusion criteria were: 1) mild cognitive impairment or dementia (>24 on Mini Mental Status Exam) (Folstein et al., 1975), 2) current alcohol abuse, major
depressive disorder (≥ 16 on 20-item Center for Epidemiologic Studies Depression Scale) (Radloff, 1977) or another psychiatric disorder, 3) history of traumatic brain injury, and 4) contraindications for MRI scanning, which may include implanted medical devices, joint replacements, and history of certain medical conditions or claustrophobia.

**Procedures**

As part of the larger WeWalk study, participants completed extensive testing prior to and at the completion of their 16-week exercise program. Measures included resting blood pressure, personal and family health history, and anthropometry, as well as a graded exercise test (described below). Participants provided written informed consent for the larger WeWalk study at an orientation session held prior to all baseline visits.

As part of the current study, participants completed a baseline MRI scan prior to beginning exercise training, and a follow-up scan within one week of finishing their exercise program. On a date prior to baseline scanning participants met with study staff to review and sign an IRB-approved consent form. Participants also completed a MRI screening document, health history form, and IQ test at this time, and were given a leisure activity questionnaire to complete at home and return at their upcoming MRI session. Participants were asked not to participate in any moderate or vigorous physical activity 48 hours prior to their MRI sessions to avoid any acute effects of exercise on cognitive performance.

All MRI images were acquired on a Trio 3-T whole body scanner (Siemens) located at the McCausland Center for Brain Imaging (Columbia, SC). In all MRI sessions we acquired a high-resolution T1-weighted structural scan (volume TR = 1960 ms, TE = 4.43 ms, 8 degree flip angle, 176 coronal slices, slice- matrix size = 256 × 208,
slice thickness = 1.0 mm, voxel size = 1 × 1 × 1, and three 10.5 minute functional runs per scanning session (repetition time [TR] = 1950 ms, echo time [TE] = 30 ms, flip angle = 90°, 34 contiguous slices at 3 mm skip 1 mm, in-plane resolution of 128 x128 pixels reconstructed in a field of view of 240 mm). Identical procedures were followed at both scanning sessions (baseline and follow-up). Participants received $20 at the completion of each session, and a picture of their brain on a CD (i.e., their T1-weighted scan) at the completion of their follow-up MRI session.

Measures

Aerobic Fitness. A graded exercise test (modified Astrand-Saltin protocol) (Hawkins et al., 2007; Levine & Stray-Gundersen, 1997) determined fitness, measured as maximum oxygen consumption (VO$_2$max). Before starting the test, a trained exercise physiologist measured heart rate and blood pressure and conducted a standard 12-lead ECG; ECG, heart rate, blood pressure, rating of perceived exertion, and treadmill speed and grade were recorded at each stage of the protocol. Participants performed the test at a constant, self-selected walking speed. The treadmill grade was increased 2% every 2 minutes until volitional exhaustion (usually occurring 8-12 minutes after the start of the test). Study staff terminated the test early if exercise blood pressure exceeded 250/115 mmHg or if abnormal ECG tracings were observed. All tests were performed under the supervision of the WeWalk medical director.

History of Leisure Activity. A modified version of the Lifetime Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) was used to assess social engagement and mental stimulation throughout the lifespan. This questionnaire assesses educational, occupational and leisure activities (e.g., traveling, reading, playing musical
instruments) in young adulthood (13-30y), midlife (30-60y) and late life (60y+). For the current study, the maximum possible score on this questionnaire is estimated at 215.

**Intelligence.** The Wechsler Abbreviated Scale of Intelligence, two-subtest form was used to obtain a brief measure of intelligence (WASI FSIQ-2) (Psychological Corporation, 1999). This abbreviated measure can be issued in 15 minutes, and includes a vocabulary test and a matrix-reasoning test. The vocabulary test assesses word knowledge, verbal concept formation, and fund of knowledge and is considered a test of crystalized abilities and general intelligence. The tester transcribed the participants’ responses verbatim and a licensed clinical psychologist assisted study staff in scoring. The matrix-reasoning test assesses visual information processing and abstract reasoning skills and is considered a test of nonverbal fluid reasoning and general intellectual ability. For this test, participants select the missing portion of a pattern from five possible choices (responses are objective [correct or incorrect]). Vocabulary and matrix-reasoning scores were combined to obtain IQ score. Scores can range from 55 to 157 on this test; scores of 90-110 correspond to average intelligence.

**Cognitive Reserve.** A delayed-match-to-sample working memory task was used in the scanner to assess cognitive reserve (see Figure 1). During each 10.5 minute functional run, participants were continuously presented with sets of one, three, or six capital letters for three seconds, followed by a single lowercase letter recognition probe seven seconds later (a crosshair was displayed in the center of the screen during the seven second rehearsal period). Participants responded ‘yes’ or ‘no’ with a left or right button press indicating whether or not the probe letter was part of the previous set. This letter memory task (Habeck et al., 2005; Steffener et al., 2012; Stern et al., 2008; Zarahn et al.,
2007), as well as a similar working memory task using abstract shapes (Habeck et al., 2003; Holtzer et al., 2009; Scarmeas et al., 2003; Stern et al., 2005; Stern et al., 2008; Stern et al., 2003), has been utilized in multiple MRI investigations of cognitive reserve mechanisms. The internal manipulation of difficulty (i.e., changes in memory load) is ideal for studying how neural processing changes in the face of a challenge. Changes in task-related network activation during low versus high-demand trials were used to indicate changes in cognitive reserve with exercise training. Gains in efficiency would be indicated by a smaller difference in task-related brain activation during low versus high-demand working memory trials at the completion of training as compared to baseline. In contrast, gains in capacity would be indicated by a larger difference in task-related brain activation at the completion of training, driven by increased activation on the high-demand trials.

Cognitive Performance. We measured how quickly participants responded to the recognition probe during performance of the delayed-match-to-sample working memory task (during fMRI scanning). Reaction time slope with increasing set size is an indicator of working memory scanning speed (Stern, 2009). Change in average reaction time slope (averaged over the 3 sets per scanning session) was used as an indicator of cognitive performance.

Analyses

MRI data were analyzed using SPM8, a MATLAB based software package specifically designed to analyze brain imaging data (www.fil.ion.ucl.ac.uk/spm/). All data were preprocessed using standard SPM protocols (realignment, coregistration, normalization and smoothing). Brain areas involved in the performance of each task
condition (i.e., 6-, 3-, and 1-letter trials) were identified using baseline data. Next we modeled the following events in a first-level analysis: high-demand trials (6-letter trials) and low-demand trials (1-letter trials). For each individual participant we calculated a statistical parametric map that subtracted brain activation during low-demand trial performance from activation during high-demand trial performance to identify the areas where the BOLD signal changed with increasing cognitive demand. These first-level analyses were conducted on both baseline and post-exercise scans, and focused specifically on activity during the retention phase of each trial (rather than the encoding or recognition phase). Next we created models for each individual participant that compared changes in brain activation (high-demand minus low-demand) at post scan and pre scan (post minus pre). These maps were entered into a second-level random-effects (group) analysis, and parameter estimates for changes in BOLD activation (p<0.001) with exercise training were extracted. To better understand what may account for any change in the differential between low- and high-demand brain activation with exercise training, we also modeled and compared each task condition versus the rest condition at both pre- and post-exercise training.

For reaction time analyses, reaction times corresponding with response errors were removed, and means and standard deviations for 1-, 3-, and 6-letter sets (across all 3 runs) were calculated. Reaction times ≥2 standard deviations from their respective means were then also removed. Reaction time slope with increasing set size (1 to 3 to 6 letters) was calculated using the 1-, 3- and 6- letter mean reaction time values for both baseline and post-exercise scanning data.
Descriptive statistics (e.g., means, frequencies) and Pearson’s correlations were run in SAS, version 9.3 (SAS Institute, Inc., Cary, NC). Due to the small sample size, all participants, regardless of their randomization assignment (high or low), were analyzed as a single group. Correlational analyses examined the relationship between change in task-related brain activation (extracted from SBM analyses) and change in fitness and reaction time slope. Residualized changes scores were calculated in place of simple change scores for the fitness and reaction time variables in correlation analyses. Although the sample size was too small to control for covariates, data were divided using median splits to look for trends relating the observed changes in brain activation with the following variables of interest: age, baseline fitness, randomization group (high or low), IQ, lifetime experience, and family history of dementia.

Results

Demographics

Although 17 participants underwent baseline MRI scanning, 3 participants dropped out of the greater WeWalk study (2 due to injuries unrelated to the exercise training program, 1 due to time/scheduling conflicts), 1 participant did not complete follow-up scanning (family emergency), and 1 participant’s post-exercise data were lost due to a staff error during data collection. Of the 12 participants that completed both pre- and post-exercise scanning, 100% completed 6 or more supervised exercise sessions in the last 2 weeks of training; average caloric expenditure per session was within 10% of the target volume for 75% of participants.

Table 1 displays baseline characteristics of participants that completed both pre- and post- exercise scanning (n=12). Participants averaged 63 years old, and 100% were
white. Average VO$_2$\textsubscript{max} was 21.9 ml/kg/min, which is considered poor to very poor for women ages 60-69, and poor for women ages 70-79 (American College of Sport Medicine, 2010). Average IQ was 119, which falls within the 90th percentile.

**Aerobic Fitness**

Average fitness level increased from 21.9 (4.1) ml/kg/min at baseline to 23.9 (4.1) ml/kg/min at follow-up, although this improvement was not significantly significant ($t=2.06$, $p=0.0634$).

**Cognitive Performance**

Cognitive performance (measured as reaction time slope) did not improve with exercise training ($t=-0.07$, $p=0.9470$). There was no correlation between change in aerobic fitness and change in reaction time slope ($r=-0.42$, $p=0.1733$).

**Changes in Brain Activation**

Table 2 lists the brain areas involved during the rehearsal phase of the task by trial type (6-, 3- and 1- letter trials). At a significance threshold of $p=0.001$ and an activation cluster size threshold of $k=10$, brain areas responding more robustly during the high-demand (compared to the low-demand) task condition after exercise training included left inferior frontal gyrus, left cuneus, right rolandic operculum, left middle temporal gyrus, left postcentral gyrus, left superior medial frontal, left inferior frontal gyrus pars orbitalis, left superior frontal gyrus, right caudate, right inferior temporal gyrus (see Table 3, Figure 2). Figure 3 provides a demonstration of the task-related BOLD signal observed by task condition before and after exercise training in four of these brain regions (left inferior frontal gyrus, left superior medial frontal gyrus, left inferior frontal gyrus pars
orbitalis, and left superior frontal gyrus). At a threshold of $p=0.001$, no brain areas responded less robustly after exercise training.

There were no significant correlations between change in task-related brain activation and change in cognitive performance (reaction time slope) with exercise training ($r$ values < 0.49). There were also no significant correlations between change in change in task-related brain activation and change in aerobic fitness ($r$ values < 0.40).

When we divided the sample, there were no differential changes in task-related brain activation by median age, baseline fitness level, or lifetime experience score ($p$s>0.1274). There were also no differential changes between those with and without a family history of dementia. Participants in the low-exercise group ($n=7$) saw a greater increase in left cuneus activation with training ($t=-2.58$; $p=0.0277$) as compared to those in the high-exercise group ($n=5$).

**Discussion**

In the current study, a brief period of exercise training led to changes in task-related brain activation in healthy older women, although not as originally hypothesized. Although we expected to see lesser differences in task-related activation between high- and low-demand task conditions after exercise training, we actually saw greater differences (i.e., increases in BOLD signal rather than decreases). Albeit in the wrong direction, we did observe changes in task-related brain activation in many frontal brain regions (e.g., left inferior frontal gyrus, left superior frontal gyrus), as hypothesized. There was no relationship between increased activation and improved task performance (measured as reaction time slope) in any task-related brain region.
Previous neuroimaging studies informed the hypothesis that exercise-induced cognitive reserve would manifest as increased brain efficiency in our sample (Scarmeas et al., 2003; Stern et al., 2005). In particular, a 2003 PET study by Scarmeas et al found that young adults with high levels of cognitive reserve (measured as high education/IQ) showed relatively large increases in brain activity with increasing task demand (more shapes to remember) whereas older adults with high levels of cognitive reserve showed relatively small increases (Scarmeas et al., 2003). This finding suggests that cognitive reserve may present differently in the face of age-related neural changes, and we applied this knowledge in hypothesizing that exercise-induced cognitive reserve may also manifest as greater efficiency in older adults. Interestingly, we found the opposite. With exercise training, participants showed increased activity in task-related brain areas, suggesting possible increased neural capacity, not efficiency.

Neural capacity is one of three mechanistic pathways within Stern’s umbrella term ‘neural reserve’ (Stern, 2006). Neural reserve refers to inter-individual variation in the efficiency, capacity or flexibility of brain networks subserving cognitive functions in the healthy brain. A brain that is more efficient (i.e., requires fewer neural resources), capable (i.e., can recruit more neural resources) and/or flexible (i.e., can use multiple networks to accomplish the same task) is thought to be less susceptible to disruption when met with a challenge. It is possible that our ‘older adult’ sample was not old enough to start employing the efficiency mechanism observed in the Scarmeas et al study. It is also possible that exercise-induced cognitive reserve has completely different mechanisms than cognitive reserve ‘built’ through mental or social activity. It should also be noted that the current study assessed only the efficient and capacity mechanisms
of the neural reserve pathway, and thus it possible that exercise also led to unmeasured increases in neural flexibility.

In the current study, changes in the brain occurred without any corresponding improvement in cognitive performance, measured as reaction time slope. These null findings may still be in line with the greater cognitive reserve theory, as it is likely that increasing the brain’s resiliency (by increasing cognitive reserve) will not necessarily translate to immediate behavioral benefits in healthy participants, but may be important later in older adulthood and especially in the face of advancing pathology. Regardless, the lack of even a slight relationship between brain-level changes and behavioral changes necessitates that the findings be interpreted with caution.

Although no other exercise intervention has used the shape or letter Sternberg task to test cognitive reserve theory, many studies have used fMRI to study the brain-level changes that occur with exercise training. Of studies using an executive functioning task, some have reported increases in task-related brain regions with exercise training/higher fitness (Liu-Ambrose et al., 2012; Prakash et al., 2011; Rosano et al., 2010) and some have reported decreases (Voelecker-Rehage et al., 2010, 2011). One study reported both increases and decreases in different areas with training (Colcombe et al., 2004). In memory studies, most researchers report increases in brain activity with exercise training (Holzschneider et al., 2012; Nagamatsu et al., 2012; Pereira et al., 2007; Smith et al., 2011), although in one study, resistance, but not aerobic, training improved cognitive performance and increased brain activity (Nagamatsu et al., 2012). In another study, fitness was related to increased brain activation during spatial memory performance, but only when participants also received spatial training (Holzschneider et al., 2012). These
conflicting findings are hard to reconcile. In general, authors that find increases in activity explain that fit older adults have an increased ability to engage task-relevant brain areas, whereas authors that find decreases claim that fit older adults are more efficient in their brain processing and require less compensation (i.e., their brains work more like young brains). Voelcker-Rehage and colleagues explain that both increases and decreases may reflect positive exercise-induced changes in brain function, and that differential findings may be due to differences in cognitive load, amount of practice in completing the task, and sample characteristics, as well as participants’ use of different cognitive strategies (Voelcker-Rehage & Niemann, 2013).

A growing evidence base supports the connection between leading an active lifestyle and reduced dementia risk. In 2008, Rolland and colleagues conducted a systematic review of longitudinal epidemiological studies linking physical activity and risk of cognitive decline, dementia or AD (Rolland, 2008). Relevant studies dated back to 1991, and of the 24 studies reviewed, 20 showed a significant protective effect of physical activity against cognitive decline or dementia. Follow-up periods ranged from 2 to 21 years, and most assessed physical activity as self-reported leisure time physical activity. Since the Rolland review, multiple longitudinal studies have found the same protective relationship when using objective measures (i.e., accelerometry, doubly labeled water, direct calorimetry) to study the physical activity-dementia risk relationship (Buchman et al., 2012; Middleton et al., 2011).

Despite the lack of paired brain and behavioral changes in the current study, a discussion of plausible mechanisms explaining the brain-level changes is warranted. Enhanced neuroplasticity and reduced cardiovascular and metabolic risk factors are often
cited as major contributors to the brain benefits of exercise training. At the cellular level, exercise has been shown to increase dendritic length, dendritic complexity, and spine density in the hippocampus, particularly in the dentate gyrus. With these changes come increases in synaptic proteins, glutamate receptors, and growth factors, all which promote synaptic plasticity, and, therefore, learning. In addition to priming pre-established neurons for learning, hippocampal neurogenesis is one of the most replicated cellular-level changes found in exercise studies. Brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1) and vascular endothelial-derived growth factor (VEGF) are key molecules thought to be highly responsible for exercise-induced neuroplasticity. Peripherally, many risk factors for cardiovascular disease and diabetes are also risk factors for dementia, especially hypertension and glucose intolerance (Cotman et al., 2007; Rolland, 2008). Hypertension is one of the greatest risk factors for white matter damage, which has been associated with decrements in executive functioning and memory (Buckner, 2004). Cognitive reserve may even be mediated by ‘vascular reserve’ or an increased ability to offset the vascular oxidative stress and reduced cerebral blood flow caused by early AD pathology (Lange-Asschenfeldt & Kojda, 2008).

**Limitations**

The major limitations of our study are the very small sample size and lack of control group. In particular, the lack of control group made it impossible to determine whether the changes observed in the brain were beneficial, exercise-induced adaptations that relate to function. The sample was also very sharp (e.g., high average IQ, highly educated), white, and female, which limits generalizability to other populations. The
high average IQ and education levels may have also limited the effects observed in this study, as our sample likely already had a great amount of ‘mental activity’-induced cognitive reserve built up at baseline. This may have, perhaps, led to some degree of a ceiling effect. It would be interesting to see if higher risk samples (e.g., lower education, lower MMSE score) might see greater gains in neural capacity with the same amount of exercise training. Lastly, the current study tested only a proposed implementation of cognitive reserve in the brain. Unfortunately, with only an immediate post-exercise assessment, we do not know if the observed changes in the brain will actually reduce dementia risk in this sample of women.

Conclusions and Future Directions

Unless new ways to prevent and treat AD are quickly discovered and implemented, a projected 7.1 million Americans will have AD by 2025 (Alzheimer's Association, 2014). This is an astounding 40% increase from today’s prevalence rate. While we hope that current national endeavors, such as the National Alzheimer’s Project Act (Department of Health and Human Services, 2011) and the National Plan to Address Alzheimer’s Disease (Department of Health and Human Services, 2012), are successful in rapidly advancing treatment development, we believe that investigations testing cognitive reserve theory could be key to prevention efforts. The concept of cognitive reserve is exciting because it suggests that, through our lifestyle choices, we have a degree of control over how our brain’s age, and, in theory, whether or not our cognitive function is preserved in the face of underlying AD pathology. As the brain-level changes observed in the current study did not translate to cognitive improvements, our conclusion that exercise-induced cognitive reserve may manifest as increased neural capacity (rather
than efficiency) in older women is speculative. Future exercise trials should build on the current findings with a larger, controlled study designs and extended follow up periods.

Acknowledgements

This work was supported by a SPARC Graduate Research Fellowship from the Office of the Vice President for Research at the University of South Carolina, a M-Fund award from the McCausland Center for Brain Imaging, and NIH R00AG031297. Katie Becofsky was also supported, in part, by a cooperative agreement from the Centers for Disease Control and Prevention (CDC) Healthy Aging Program through the Prevention Research Center Program, U48-DP-001936, SIP 09-027. The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Department of Health and Human Services. The authors would also like to thank Davis ‘Brian’ Berry, Philip Riddle, and the WeWalk study staff, especially Kim Bowyer and Madison DeMello, for their help with the project. We would also like to thank Scott Vendemia for his assistance with MRI scanning, as well as all study participants for making this project possible.
Table 4.1 Baseline demographic characteristics (n=12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Average (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.4 (4.3)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.6 (2.8)</td>
</tr>
<tr>
<td>VO₂max (ml/kg/min)</td>
<td>21.9 (4.1)</td>
</tr>
<tr>
<td>MMSE⁠a</td>
<td>28.9 (1.7)</td>
</tr>
<tr>
<td>CESD⁠b</td>
<td>5.7 (7.8)</td>
</tr>
<tr>
<td>LEQ³</td>
<td>108.5 (23.2)</td>
</tr>
<tr>
<td>WASI⁠d</td>
<td>119.4 (10.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>12 (100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annual Income</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;19,999</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>20-000-49,999</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>50,000-79,999</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>80,000+</td>
<td>5 (41.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High School graduate</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Some college</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>College graduate</td>
<td>7 (58.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exercise group</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Family history of Dementia (yes/no)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>No</td>
<td>7 (58.3)</td>
</tr>
</tbody>
</table>

a MMSE=Mini Mental Status Exam
b CES-D= Center for Epidemiologic Studies Depression Scale
c LEQ=Lifetime Experience Questionnaire
d WASI= Wechsler Abbreviated Scale of Intelligence, two-subtest form
Table 4.2  Brain networks involved during rehearsal of the 1-, 3- and 6-letter sets (1-, 3-, or 6-letter task minus rest) at baseline.

<table>
<thead>
<tr>
<th>Region</th>
<th>L/R</th>
<th>Local Maxima Peak Coordinates (MNI)</th>
<th>Cluster Size</th>
<th>T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td><strong>6-Rest:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>R</td>
<td>20</td>
<td>-70</td>
<td>62</td>
</tr>
<tr>
<td>Supplementary Motor Area</td>
<td>L</td>
<td>-2</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td>Cuneus</td>
<td>L</td>
<td>-2</td>
<td>-92</td>
<td>18</td>
</tr>
<tr>
<td>IFG^e</td>
<td>R</td>
<td>36</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>L</td>
<td>-38</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>L</td>
<td>-52</td>
<td>-62</td>
<td>2</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>R</td>
<td>32</td>
<td>-18</td>
<td>58</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>L</td>
<td>-26</td>
<td>-68</td>
<td>52</td>
</tr>
<tr>
<td>Vermis</td>
<td>2</td>
<td>-62</td>
<td>-14</td>
<td></td>
</tr>
<tr>
<td>Calcarine Sulcus</td>
<td>R</td>
<td>16</td>
<td>-78</td>
<td>14</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>R</td>
<td>42</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus pars opercularis</td>
<td>L</td>
<td>-38</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td><strong>3-Rest:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>L</td>
<td>-40</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>L</td>
<td>-34</td>
<td>-14</td>
<td>52</td>
</tr>
<tr>
<td>Postcentral Gyrus</td>
<td>L</td>
<td>-50</td>
<td>-26</td>
<td>56</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>L</td>
<td>-50</td>
<td>-64</td>
<td>0</td>
</tr>
<tr>
<td>Precentral Gyrus</td>
<td>R</td>
<td>46</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Insula</td>
<td>R</td>
<td>34</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Supplementary Motor Area</td>
<td>L</td>
<td>-2</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>Angular Gyrus</td>
<td>R</td>
<td>32</td>
<td>-64</td>
<td>44</td>
</tr>
<tr>
<td>Putamen</td>
<td>L</td>
<td>-22</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>L</td>
<td>-14</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>L</td>
<td>-28</td>
<td>-68</td>
<td>50</td>
</tr>
<tr>
<td>IFG pars Triangularis</td>
<td>L</td>
<td>-32</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Insula</td>
<td>L</td>
<td>-34</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td><strong>1-Rest:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>L</td>
<td>-30</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>L</td>
<td>-24</td>
<td>-68</td>
<td>50</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>L</td>
<td>-40</td>
<td>32</td>
<td>30</td>
</tr>
</tbody>
</table>

^aL= left hemisphere, R= right hemisphere  
^bMNI=Montreal Neurological Institute  
^cExtent threshold k = 20  
^dT-value: local maxima thresholded at p < 0.05 FWE corrected  
^eIFG=inferior frontal gyrus
Table 4.3 Brain regions responding more robustly to high- versus low-demand trials (6-1) after exercise training.

<table>
<thead>
<tr>
<th>Region</th>
<th>L/R</th>
<th>Local Maxima Peak Coordinates (MNI)</th>
<th>Cluster Size</th>
<th>T-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Cuneus</td>
<td>L</td>
<td>-10</td>
<td>-68</td>
<td>28</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>L</td>
<td>-46</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>Rolandic Operculum</td>
<td>R</td>
<td>60</td>
<td>-10</td>
<td>14</td>
</tr>
<tr>
<td>Middle Temporal Gyrus</td>
<td>L</td>
<td>-44</td>
<td>-68</td>
<td>16</td>
</tr>
<tr>
<td>Postcentral Gyrus</td>
<td>L</td>
<td>-58</td>
<td>-10</td>
<td>16</td>
</tr>
<tr>
<td>Superior Medial Frontal Gyrus</td>
<td>L</td>
<td>-14</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus pars orbitalis</td>
<td>L</td>
<td>-28</td>
<td>54</td>
<td>-2</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>L</td>
<td>-14</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Caudate</td>
<td>R</td>
<td>10</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Inferior Temporal Gyrus</td>
<td>R</td>
<td>50</td>
<td>-50</td>
<td>-2</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>L</td>
<td>-44</td>
<td>26</td>
<td>16</td>
</tr>
</tbody>
</table>

\( ^a \)L= left hemisphere, R= right hemisphere  
\( ^b \)MNI= Montreal Neurological Institute  
\( ^c \)Extent threshold k = 10  
\( ^d \)T-value: local maxima thresholded at p < 0.001
Figure 4.1 Delayed Match to Sample Letter Sternberg fMRI task. Participants underwent three 10.5 minute fMRI runs during which they were randomly presented with sets of 1, 3 and 6 capital letters, each followed by a 7 second delay (rehearsal period) and a single lower-case recognition probe letter. Participants were asked to press a button to indicate whether the probe letter was part of the original set (yes/no).
Figure 4.2 Task-related brain regions responding more robustly with greater cognitive demand (6-1) after exercise training. Maps present brain activation thresholded at $p < 0.001$. 
Figure 4.3 Change in task-related BOLD signal with exercise training by task condition in four frontal regions.

a Inferior Frontal Gyrus
b Superior Frontal Gyrus
Chapter 5: The Cognitive Effects of a Supervised
16-week Walking Intervention in Healthy Older Women

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2 Becofsky, K.M., Newman-Norlund, R., Wang, X. & Wilcox, S. To be submitted to Psychology and Aging
Abstract

Walking initiatives are being promoted for environmental, transportation, and general health purposes. With the rapid aging of the American population, it is important and timely to investigate the cognitive benefits of walking. The current study used a quasi-experimental design (pre-post design with an intervention and matched control group) to investigate the cognitive effects of a supervised, 16-week walking intervention in healthy older women. Intervention participants (n=17; mean age 64) completed a battery of cognitive tasks (CANTAB©) before beginning and after completing exercise training; control group participants (n=18; mean age 66) completed the battery on dates approximately 16-weeks apart. There were no significant differences between the groups on any cognitive performance measures based on ANOVA analyses (ps > 0.24). Due to the small sample size, we also calculated effect sizes. Effects of the exercise intervention were small for the total trial and total error outcomes on the paired associate learning task (d=0.20 and d=0.39, respectively), as well as for the spatial span task (d=0.38). For the control group, effect sizes were small for the verbal free recall task (d=0.23), medium for the rapid visual processing (d=0.62) and paired associate learning task (d=0.71 and d=0.52 for the total trial and total error outcomes, respectively), and large for the spatial span task (d=1.02). The findings of this small study are unexpected and should not discourage research in this important area.

Keywords: Physical activity, exercise, cognition, cognitive health
The Cognitive Effects of a 16-week Supervised Walking Intervention in Healthy Older Women

In 2011, the ‘silver tsunami’ began as the first baby boomers turned 65. Today and every day though 2030, 10,000 American baby boomers will reach this aging milestone (Pew Research Center, 2010). By 2030, more than 70 million Americans, representing almost 20% of the population, will be 65 or older (U.S. Department of Health and Human Services, 2011). As advanced age is the greatest risk factor for Alzheimer’s disease, brain and cognitive health promotion efforts are now at the forefront of the US public health agenda (Department of Health and Human Services, 2011, 2012).

Separately but simultaneously underway is a national movement to promote walking (everybodywalk.org; AmericaWalks.org). Walking initiatives are promoted for environmental, transportation, and general health purposes. It is also important and timely to specifically investigate the cognitive benefits of walking in advanced age. A growing body of evidence from both epidemiologic studies (Bowen, 2012; Buchman et al., 2012; Rolland, 2008) and randomized controlled trials (Baker et al., 2010b; Colcombe & Kramer, 2003; Lautenschlager, 2008) supports physical activity as a means to promote cognitive health in aging, yet few studies have focused exclusively on testing the cognitive benefits of moderate-intensity walking.

The current study used a quasi-experimental design (non-randomized, pre-post design with an intervention and matched control group) to determine the cognitive effects of a supervised 16-week walking intervention in healthy older women. We hypothesized that participants in the walking program would improve on a variety of cognitive tasks as compared to the control participants; we expected
to see the greatest differential between groups on tasks that rely on executive function capabilities (i.e., spatial span, rapid visual processing). We also hypothesized that greater gains in cognitive performance would be observed in those experiencing greater gains in aerobic fitness.

Methods

Participants

Participants in the intervention group (n=22) are a sub-sample of women participating in an on-going randomized walking trial. The WeWalk study is investigating the effects of a chronic walking program on energy expenditure compensation in older women. For this study, healthy yet sedentary women (N=72) are randomized to either a higher (14 kcal/kg body weight, weekly) or lower-dose (8 kcal/kg body weight, weekly) 16-week walking program. Supervised walking is performed at a moderate intensity (60-65% VO$_2$max), 4 d/wk, on an inclined motor-driven treadmill. The difference between the higher and lower-dose programs is one of session duration; women in the higher dose program walk, on average, 55-60 minutes per session, while women in the lower dose program walk, on average, 30-35 minutes per session.

Women are recruited for the WeWalk study on a rolling basis via newspaper advertisements, flyers, university listservs, and university newsletters. Interested participants complete an initial phone screening with the study coordinator. To be eligible, women must be: 1) age 60-75 yrs, 2) body mass index (BMI) greater than 18 but less than 30 kg/m$^2$, 3) weight stable (±5%) during the previous 3 months, 4) underactive for the previous 3 months (<20 min, 3 times/week of resistance or endurance exercise), and 5) non-smoking for the past year. Exclusion criteria include: 1) self-reported
significant cardiovascular disease (e.g., cardiomyopathy, myocardial infarction), 2) other self-reported medical conditions, including but not limited to metabolic disease (e.g., diabetes), chronic or recurrent respiratory conditions, active cancer, musculoskeletal disease interfering with exercise, or any serious medical condition that may affect adherence to the protocol or exercising safely, or be aggravated by exercise, 3) medications known to affect exercise performance or metabolism (e.g., hyperthyroid medication, β-blockers, stimulants), 3) excess caffeine use (>500mg/day), 4) any self-reported contraindications to exercise according to the American College of Sports Medicine criteria (American College of Sports Medicine [ACSM], 2010).

Women were recruited in-person for the current sub-study at the first of six WeWalk baseline sessions, held approximately 4-5 weeks before exercise training began. Additional or overlapping exclusion criteria were: 1) mild cognitive impairment or dementia, 2) current alcohol abuse, major depressive disorder or another psychiatric disorder, 3) history of traumatic brain injury. Additional women from the community (n=19) were recruited through a newspaper advertisement and word of mouth to serve as a control group. These women were asked to not begin an exercise program for the duration of the study. Recruitment efforts for the control group advertised a study relating to memory and thinking skills. Individuals interested in the memory and thinking study also completed an initial screening with the WeWalk study coordinator. Inclusion/exclusion criteria were the same as the for the WeWalk study.

**Procedures**

Intervention participants completed extensive testing prior to and at the completion of their 16-week walking program. Measures included resting blood pressure,
personal and family health history, and anthropometry, as well as a graded exercise test. We used the Mini Mental Status Exam (Folstein, Folstein & McHugh, 1975; [MMSE]) to screen for dementia (< 24). We used the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) to assess depressive symptoms. Intervention participants provided written informed consent to participate in the larger WeWalk study at an orientation session held prior to all baseline visits.

As part of the current sub-study, participants completed a baseline cognitive testing session prior to beginning exercise training, and a follow-up session within one week of finishing their walking program. At these sessions, participants performed a series of computerized, touch-screen tasks to assess performance in different cognitive domains. At the baseline session, participants also filled out a brief health history form, completed an IQ test, and were given a leisure activity questionnaire to complete at home and turn in at an upcoming exercise session. We asked participants not to participate in any moderate or vigorous physical activity 48 hours prior to their cognitive testing sessions to avoid any acute effects of exercise on cognitive performance. Participants reviewed and signed a consent form approved by the university’s institutional review board upon arriving at their baseline cognitive testing session. All participants were compensated $20 per session.

Participants in the control group followed near identical cognitive testing procedures, completing their two sessions approximately 16 weeks apart. Prior to their baseline session we mailed a packet of questionnaires (completed by the intervention group as part of WeWalk participation), which participants completed and brought with them to their baseline session. We conducted dementia screening using the MMSE at the
baseline session. We measured height, weight and blood pressure at baseline, and weight and blood pressure again at post-testing. Height was measured with a Seca mobile stadiometer to the nearest quarter inch. Weight was measured with Seca scale to the nearest tenth of a pound. Blood pressure was measured using an Omron Automatic Blood Pressure Monitor (Model HEM-780). We asked control group participants not to begin a structured exercise program in the 16 weeks between sessions.

Measures

Aerobic Fitness. A graded exercise test (modified Astrand-Saltin protocol (Hawkins et al., 2007; Levine & Stray-Gundersen, 1997) determined fitness, measured as maximum oxygen consumption (VO$_{2}$max), for intervention participants. Before starting the test, a trained exercise physiologist measured heart rate and blood pressure and conducted a standard 12-lead ECG; ECG, heart rate, blood pressure, rating of perceived exertion, and treadmill speed and grade were recorded at each stage of the protocol. Participants performed the test at a constant, self-selected walking speed. The treadmill grade was increased 2% every 2 minutes until volitional exhaustion (usually occurring 8-12 minutes after the start of the test). Study staff terminated the test early if exercise blood pressure exceeded 250/115 mmHg or if abnormal ECG tracings were observed. All tests were performed under the supervision of the WeWalk medical director. Control participants did not undergo graded exercise testing.

History of Leisure Activity. A modified version of the Lifetime Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007) assessed mental stimulation and social engagement throughout the lifespan. This questionnaire assesses educational, occupational and leisure activities (e.g., speaking foreign language, traveling, playing
musical instruments) in young adulthood (13-30y), midlife (30-60y) and late life (60y+). For the current study, the maximum possible score on this questionnaire is estimated at 215.

**Intelligence.** The Wechsler Abbreviated Scale of Intelligence, two-subtest form was used to obtain a brief measure of intelligence (WASI FSIQ-2) (Psychological Corporation, 1999). This abbreviated measure can be issued in 15 minutes, and includes a vocabulary test and a matrix-reasoning test. The vocabulary test assesses word knowledge, verbal concept formation, and fund of knowledge and is considered a test of crystalized abilities and general intelligence. The tester transcribed the participants’ responses verbatim and a licensed clinical psychologist assisted study staff in scoring. The matrix-reasoning test assesses visual information processing and abstract reasoning skills and is considered a test of nonverbal fluid reasoning and general intellectual ability. For this test, participants select the missing portion of a pattern from five possible choices (responses are objective [correct or incorrect]). Vocabulary and matrix-reasoning scores were combined to obtain IQ score. Scores can range from 55 to 157 on this test; scores of 90-110 correspond to average intelligence.

**Cognitive Function.** The Cambridge Neuropsychological Test Automated Battery (CANTAB®) is a series of computerized, touch-screen tasks used to assess performance in different cognitive domains. Performance in the domains tested in this study have been shown to predict rates of cognitive decline (Blacker et al., 2007; Collie et al., 2002; De Jager et al., 2005; De Jager & Budge, 2005) and/or have been shown to improve with exercise training (Colcombe & Kramer, 2003). Prior to completing the chosen battery, participants were familiarized with the touch screen using the Motor
Screening Task. This task screens for visual, movement or comprehension difficulties and takes approximately 2 minutes to complete.

*Verbal memory.* The Verbal Recognition Memory task tests free recall and recognition memory. Participants are shown a list of 12 words and asked to: 1) produce as many words as possible immediately after presentation, 2) recognize the original words from a list of 24 (12 original words, 12 distractors) immediately after free recall, and 3) recognize the original word list from another list of 24 following a 20-30 minute delay. The outcome measure used in this study was the number of words recalled immediately after presentation. This task takes about 7 minutes.

*Sustained Attention.* The Rapid Visual Information Processing task is a measure of sustained attention and general performance. During this task, digits from 2 to 9 appear in random order at the rate of 100 digits per minute; participants must detect sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and immediately press a button box. The outcome measure reported in this study is total hits (i.e., sequences detected). The task takes 7 minutes.

*Working memory.* Spatial Span was used to assess working memory capacity. For this task, a series of boxes (starting at two and increasing to nine) change color in a specific sequence. When the boxes stop changing color, participants must touch the boxes in the same sequence that they changed. Participants are given three tries to correctly replicate a sequence at each level (e.g., 2 box level, 3 box level, etc.). The outcome measure reported in this study is span length achieved. The task takes about 5 minutes.
**Visuospatial learning.** The Paired Associates Learning task is a challenging test of visual memory and new learning. During this task, boxes around the perimeter of the screen are opened and closed in random order. One or more of the boxes (up to eight) will reveal a pattern. When all boxes have opened and closed, the pattern or patterns that were revealed are displayed in the middle of the screen, and the participant must touch the box where each pattern was originally seen. Participants get 10 tries to correctly locate the patterns in each stage (e.g., one pattern to locate, three patterns to locate, etc.). Outcome measures include total errors and total trials to locate all patterns. The task takes about 10 minutes.

**Analyses**

We performed analyses using SAS, version 9.3 (SAS Institute, Inc., Cary, NC). Basic descriptive statistics included frequencies and means of key variables. PROC UNIVARIATE tested the distribution and skewness of these variables. Chi-square and t-tests assessed differences between groups at baseline. We created residualized change scores for change variables (e.g., changes in fitness, cognitive performance) and used them instead of simple change scores in all ANOVA and correlation analyses.

ANOVA determined whether performance on any of the cognitive tasks (rapid visual information processing [total hits], paired associates learning [total trials], spatial span [span length achieved], immediate verbal recall [number of correct responses]) improved with exercise training as compared to no exercise. Separate paired t-tests verified the relationship between exercise training and change in performance on each cognitive task. Due to the small sample size, we also calculated effect sizes to assess the magnitude of change in cognitive performance within and between groups.
We divided the exercise group by randomization assignment (high or low exercise group), and conducted an ANOVA to determine whether there were differential changes in cognitive performance based on exercise dose (high, low, no exercise [control]). The exercise group was also divided based on age, baseline fitness, lifetime experience (median splits), and family history of AD (yes/no) to look for trends relating to changes in cognitive performance (t-tests). For each cognitive task, Pearson’s correlation determined whether change in aerobic fitness was associated with change in cognitive performance in intervention participants.

**Results**

Four participants dropped out of the greater *WeWalk* study after baseline testing (2 due to injuries unrelated to the exercise training program, 2 due to time/scheduling conflicts), one participant finished *WeWalk* but did not return for follow-up cognitive testing (family emergency), and one participant dropped out of the control group (time conflict). Exercise training compliance data were available for 15 of 17 intervention participants. During the last 2 weeks of training, 93% of these participants (n=14) completed 6 or more supervised exercise sessions. Average caloric expenditure per session was within 10% of the target volume for 80% of these participants (n=12).

Table 1 displays baseline characteristics of study participants included in pre-post analyses (n=35). Participants in the intervention group (n=17) averaged 64 years old, and 94% were white. Average VO₂max was 20.6 ml/kg/min, which is considered poor to very poor for women ages 60-79 (American College of Sport Medicine, 2010). Participants in the control group (n=18) averaged 66 years old, and 94% were white.
Average IQ was 116 for the exercise group and 114 for the control group, ranking them in the 86th and 82nd percentile, respectively.

Baseline cognitive performance did not differ between groups on any CANTAB© task (ps > 0.11). As displayed in Table 2, there were no significant changes in cognitive performance in the intervention group (ps > 0.16). The control group increased their spatial span length, had more total hits on the rapid visual processing task, and required fewer trials and made fewer errors on the paired associate learning task at follow-up (ps < 0.05). As shown in Table 3, there were no significant differences between the exercise and control groups on any cognitive performance measures based on ANOVA analyses (ps > 0.14). There were also no differential changes in cognitive performance when comparing the high, low, and no exercise groups (ps > 0.24).

As shown in Table 4, pre-post effect sizes for the exercise intervention group were small for the paired associate learning total trial and total error outcomes (d=0.20 and d=0.29, respectively), as well as for the spatial span task (d=0.38). For the control group, effect sizes were small for the verbal free recall task (d=0.23), medium for the rapid visual processing (d=0.62) and paired associate learning task (d=0.71 and d=0.52 for the total trial and total error outcomes, respectively), and large for the spatial span task (d=1.02).

Sixteen of the seventeen participants in the exercise training group had post-training fitness data available. Average VO2max increased from 20.6 (4.0) ml/kg/min at baseline to 22.1 (5.2) ml/kg/min after training, although this improvement was not statistically significant (t=-1.48, p=0.1596). There was no significant correlation between
change in fitness and change in performance on any cognitive outcomes (r values < .25, ps > 0.35).

Older participants (>62 years) improved more on the rapid visual processing task after exercise training as compared to younger participants (≤62 years) (t=-3.05; p=0.0087). Participants reporting no family history of dementia (n=11) improved more on the rapid visual processing task (t=-2.55; p=0.0223) compared to participants reporting a family history of dementia (n=6). There was a trend toward those with lower fitness at baseline (≤19.9 ml/kg/min) also improving more on this task compared to those with higher fitness at baseline (>19.9 ml/kg/min) (t=1.90, p=0.0767). Change in cognitive performance did not differ based on exercise level (high or low) or Lifetime Experience Questionnaire score.

**Discussion**

This study sought to make a contribution to the exercise science and public health literature as a controlled study of the cognitive effects of a supervised, moderate-intensity walking. This study is timely; there are on-going national efforts aimed to increase walking levels in the US, yet it is unknown whether these efforts might be helpful to contemporaneous efforts to promote healthy cognitive aging. The results of this study were unexpected. We found no differences in change in cognitive performance between the exercise and control groups. There were also no differential changes in cognitive performance when participants were divided into three levels of exercise training (high exercise, low exercise, no exercise [control]). Further, although the walking intervention yielded small positive effects on the spatial learning task and large positive effects on the
spatial span working memory task, we observed even greater effects across multiple tasks in control group participants.

Multiple factors may have led to the unexpected effects observed in control participants. First, there was less time between cognitive testing sessions in control participants compared to intervention participants. All control participants came in for their follow-up cognitive testing session 4-4.5 months after their initial visit; the length of time between visits was set based on the length of the walking program. Importantly, the WeWalk program was extended to incorporate a holiday break, as well as various unpredictable events, such as participant illnesses, travel, and deaths in family. Although extending the program allowed for better retention rates, cognitive testing sessions were separated by more than 5 months for 5 participants, and by more than 6 months for 4 participants. The lesser length of time between sessions may have led to greater practice effects in control participants. Practice effects have been shown in prior investigations of the psychometric properties of the CANTAB© (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004; Lowe & Rabbitt, 1998), although time between test and re-test was much shorter in these studies (4 weeks). Of note, Lowe & Rabbitt (1998) stress that practice effects may be more problematic in tests of executive function, as performance can abruptly improve once an optimal strategy is adopted (and therefore these tests only truly ‘work’ when they are novel). Importantly, all four CANTAB© tasks used in the current study involved a degree of executive functioning.

Additionally, as the control group was recruited separately, it is possible that advertisements for the control group as a memory and thinking study (as opposed to an exercise study) attracted volunteers who were worried about their memory and were more
motivated to improve their performance at their follow-up visit. It is also possible that control participants, if indeed they were more concerned about memory loss, may have been more likely to seek out other ‘brain training’ activities (e.g., Lumosity) between sessions, which could also partially explain their improved performance. Participants were not asked about participation in ‘brain training’ activities.

Lastly, an experimenter bias may have negatively affected the performance of intervention group participants at follow-up. While control participants only met with the primary investigator on two occasions, intervention group participants became very familiar with the investigator over the course of the 16-week intervention and may have felt pressure to improve their performance at follow-up. This pressure may have led to greater stress and lower performance, making the practice effects observed in the control group seem even more substantial.

We hope that the null results of the current study do not discourage future research in this area, as the implications of this area of research are quite large. Without preventive intervention, the potential consequences of poor cognitive aging are grim: Alzheimer’s disease already kills at rates comparable to heart disease and cancer (James et al., 2014), and rates are expected to more than triple by the year 2050 (Alzheimer's Association, 2014). Although the immediate follow-up measures employed by most randomized control trials do not allow for any analysis of future dementia risk, there are promising results from many recent longitudinal studies in exercise science. In 2012, Buchman and colleagues found that a higher level of total daily physical activity, measured for 10 days with actigraphy, was associated with a reduced risk of AD (average follow-up 4 years) (Buchman et al., 2012). A 2012 study by Middleton et al found that
total activity energy expenditure was related to risk of cognitive impairment at 2 or 5 year follow-up; older adults in the highest sex-specific tertile of activity energy expenditure had the lower odds of declining at least one standard deviation on the Modified Mini-Mental State Examination compared to those in the lowest tertile (Middleton et al., 2011).

Studies similar to the current study but with larger samples and a randomized design may be particularly important to cognitive health promotion efforts, as walking, specifically, may be easier to promote than exercise, more generally (Reis, 2008). Walking is safe and easy for older adults, and often requires very minimal cost (Lee & Buchner, 2008). It also leads to substantial health benefits (Murphy, Nevill, Murtagh, & Holder, 2007). National efforts to increase walkability will likely make walking even safer, more practical, and more enjoyable in many communities across the nation in the coming years. Findings from research in this area, in concert with environmental and policy changes to increase walkability, may lead to effective, large-scale efforts to increase physical activity adoption and adherence for cognitive health purposes.

Limitations

In addition to the alternative explanations for control group performance already discussed, more general limitations of the current study are the small sample size and lack of randomization. Although the control group was recruited separately, we tried to minimize differences between the control and intervention group by using the same recruitment venues, and ultimately the groups were not significantly different from one another at baseline (with the exception of the Lifetime Experience Questionnaire, on which the intervention group scored higher). The sample was also highly educated, white, and all female, which limits generalizability to other populations.
Conclusions and Future Directions

At a time when separate but concurrent national efforts aim to increase walking levels and promote healthy cognitive aging, this study sought to contribute to our understanding of how the latter may benefit from the former. Future research should re-test our hypotheses with a larger, randomized sample, and with a careful eye toward avoiding practice effects. An extended follow-up period would also be ideal, as it would allow for investigation of the ultimate outcome of interest (i.e., age of dementia onset, if ever). Lastly, social engagement and mental stimulation may be as important as physical activity in preserving cognitive function and reducing dementia risk (Stern 2006), and therefore multi-component interventions should be tested in pursuit of maximizing cognitive benefits; the Experience Corps volunteer program for older adults is an excellent model of what this type of intervention looks like in community settings (Carlson et al., 2008).

Acknowledgements

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the *WeWalk* study staff for their help with the project. We would also like to thank all study participants for making this project possible.
Table 5.1 Baseline demographic characteristics (n=35).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n=17)</th>
<th>Control (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Average (SD)</td>
<td>n</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>17</td>
<td>63.9 (4.0)</td>
<td>18</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>17</td>
<td>26.2 (2.9)</td>
<td>18</td>
</tr>
<tr>
<td>VO$_2$max (ml/kg/min)</td>
<td>17</td>
<td>20.6 (4.0)</td>
<td>NA</td>
</tr>
<tr>
<td>MMSE$^a$</td>
<td>17</td>
<td>29.0 (1.6)</td>
<td>18</td>
</tr>
<tr>
<td>CES-D$^b$</td>
<td>17</td>
<td>6.5 (7.3)</td>
<td>18</td>
</tr>
<tr>
<td>LEQ$^c$</td>
<td>17</td>
<td>112.3 (29.0)</td>
<td>18</td>
</tr>
<tr>
<td>WASI$^d$</td>
<td>17</td>
<td>116.0 (11.7)</td>
<td>18</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>16</td>
<td>(94.1)</td>
<td>17</td>
</tr>
<tr>
<td>African American</td>
<td>1</td>
<td>(5.9)</td>
<td>1</td>
</tr>
<tr>
<td>Annual Income</td>
<td>15</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>&lt;19,999</td>
<td>1</td>
<td>(6.7)</td>
<td>3</td>
</tr>
<tr>
<td>20-000-49,999</td>
<td>3</td>
<td>(20.0)</td>
<td>7</td>
</tr>
<tr>
<td>50,000-79,999</td>
<td>4</td>
<td>(26.7)</td>
<td>4</td>
</tr>
<tr>
<td>80,000+</td>
<td>7</td>
<td>(46.7)</td>
<td>4</td>
</tr>
<tr>
<td>Education</td>
<td>16</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>High school graduate</td>
<td>2</td>
<td>(12.5)</td>
<td>2</td>
</tr>
<tr>
<td>Some college</td>
<td>5</td>
<td>(31.3)</td>
<td>6</td>
</tr>
<tr>
<td>College graduate</td>
<td>9</td>
<td>(56.3)</td>
<td>10</td>
</tr>
<tr>
<td>Family History of Dementia</td>
<td>17</td>
<td>18</td>
<td>0.23</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----</td>
<td>----</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(yes/no)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>10</td>
<td>55.6</td>
</tr>
<tr>
<td></td>
<td>(35.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>8</td>
<td>44.4</td>
</tr>
<tr>
<td></td>
<td>(64.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. *= statistically significant at p<.05

*a* MMSE=Mini Mental Status Exam  
*b* CES-D= Center for Epidemiologic Studies Depression Scale  
*c* LEQ=Lifetime Experience Questionnaire  
*d* WASI= Wechsler Abbreviated Scale of Intelligence, two-subtest form
Table 5.2 Change in CANTAB\textsuperscript{c} task performance by group\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>Baseline</th>
<th>Post</th>
<th>t value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise Group (n=17)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Free Recall- Total Correct</td>
<td>8.1 (1.4)</td>
<td>8.3 (1.7)</td>
<td>-0.75</td>
<td>0.4636</td>
</tr>
<tr>
<td>Spatial Span- Span Length</td>
<td>5.3 (0.9)</td>
<td>5.6 (0.9)</td>
<td>-1.46</td>
<td>0.1635</td>
</tr>
<tr>
<td>RVP\textsuperscript{b} - Total Hits</td>
<td>18.1 (5.4)</td>
<td>18.9 (3.6)</td>
<td>-0.89</td>
<td>0.3870</td>
</tr>
<tr>
<td>PAL\textsuperscript{c} - Total Trials</td>
<td>12.6 (3.3)</td>
<td>11.9 (2.1)</td>
<td>0.76</td>
<td>0.4591</td>
</tr>
<tr>
<td>PAL- Total Errors</td>
<td>12.9 (9.6)</td>
<td>10.1 (5.8)</td>
<td>1.31</td>
<td>0.2082</td>
</tr>
<tr>
<td><strong>Control Group (n=18)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Free Recall- Total Correct</td>
<td>8.4 (1.4)</td>
<td>8.7 (2.2)</td>
<td>-0.73</td>
<td>0.4760</td>
</tr>
<tr>
<td>Spatial Span- Span Length</td>
<td>5.1 (0.9)</td>
<td>5.9 (1.4)</td>
<td>-4.19</td>
<td>0.0006</td>
</tr>
<tr>
<td>RVP- Total Hits</td>
<td>15.4 (4.0)</td>
<td>17.9 (3.3)</td>
<td>-3.52</td>
<td>0.0026</td>
</tr>
<tr>
<td>PAL- Total Trials</td>
<td>14.3 (3.1)</td>
<td>12.1 (2.2)</td>
<td>4.06</td>
<td>0.0009</td>
</tr>
<tr>
<td>PAL- Total Errors</td>
<td>16.4 (10.5)</td>
<td>10.9 (6.3)</td>
<td>2.95</td>
<td>0.0094</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Paired t tests determined the significance of change in performance.  
\textsuperscript{b} RVP=Rapid Visual Processing  
\textsuperscript{c} PAL=Paired Associate Learning
Table 5.3 Group differences in change in CANTAB© task performance

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>F value</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Free Recall- Total Correct</td>
<td>0.08</td>
<td>1, 32</td>
<td>0.78</td>
</tr>
<tr>
<td>Spatial Span- Span Length</td>
<td>2.30</td>
<td>1, 33</td>
<td>0.14</td>
</tr>
<tr>
<td>RVP^b- Total Hits</td>
<td>0.05</td>
<td>1, 33</td>
<td>0.82</td>
</tr>
<tr>
<td>PAL^c- Total Trials</td>
<td>0.27</td>
<td>1, 32</td>
<td>0.61</td>
</tr>
<tr>
<td>PAL- Total Errors</td>
<td>0.01</td>
<td>1, 32</td>
<td>0.94</td>
</tr>
</tbody>
</table>

^aANOVA analyses used residualized change scores.
^bRVP=Rapid Visual Processing task
^cPAL=Paired Associate Learning task
Table 5.4 Within- and between-group effect sizes for change in CANTAB© task performance.

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>Exercise Group ES&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Control Group ES</th>
<th>Between Group ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Free Recall- Total Correct</td>
<td>0.18</td>
<td>0.23</td>
<td>0.06</td>
</tr>
<tr>
<td>Spatial Span- Span Length</td>
<td>0.38</td>
<td>1.02</td>
<td>0.60</td>
</tr>
<tr>
<td>Rapid Visual Processing- Total Hits</td>
<td>0.16</td>
<td>0.62</td>
<td>0.34</td>
</tr>
<tr>
<td>Paired Associate Learning- Total Trials</td>
<td>0.20</td>
<td>0.71</td>
<td>0.49</td>
</tr>
<tr>
<td>Paired Associate Learning- Total Errors</td>
<td>0.29</td>
<td>0.52</td>
<td>0.26</td>
</tr>
</tbody>
</table>

<sup>a</sup> ES= Effect size.
Chapter 6: Overall Summary and Conclusions

The prevention and treatment of Alzheimer’s disease (AD) is a pressing public health issue. Epidemiologic and experimental evidence suggests that exercise has a beneficial effect on cognitive health (Physical Activity Guidelines Advisory Committee, 2008). At the brain level, this association may be explained, in part, by cognitive reserve theory. Cognitive reserve theory suggests that the physically fit brain may be more efficient, flexible, and/or capable of recruiting neural resources than the unfit brain (Stern, 2009). A brain functioning in this manner is more difficult to disrupt, and therefore fit individuals should be better able to maintain their cognitive abilities despite, for example, advancing AD pathology. Researchers at Columbia University have devised a systematic approach to testing these plausible mechanisms using functional magnetic resonance imaging (fMRI) (Stern, 2009). Although there is a growing body of neuroimaging research demonstrating that the fit brain functions differently than the unfit brain, the current study was the first to study the role of exercise in building CR using this methodology.

Manuscript 1 reports, more specifically, our investigation of 1) whether participation in a 16-week walking program increased brain efficiency, and 2) whether increased brain efficiency correlated with change in fitness and cognitive performance. Twelve participants underwent fMRI scanning before and after exercise training. During fMRI scanning, participants completed the Sternberg delayed-match-to-sample letter task. Brain activation during the low-demand task condition was subtracted from brain
activation during the high-demand condition. We expected this difference to become lesser with exercise training. Within our sample (mean age 63), the difference became greater in the following brain regions with exercise training: left inferior frontal gyrus, left cuneus, right rolandic operculum, left middle temporal gyrus, left postcentral gyrus, left superior med frontal, left superior frontal gyrus, right caudate, right inferior temporal gyrus (ps < 0.001). No task-related brain regions were utilized more efficiently after exercise training (ps > 0.001). These findings suggest that exercise training may lead to greater recruitment of task-related neural resources (not greater network efficiency, as hypothesized) in this sample. As there were no observable relationships between change in task-related brain activation and change in cognitive performance (measured as reaction time slope), these findings should be interpreted with caution.

Manuscript 2 reports our investigation of the cognitive effects of a 16-week walking program. Intervention participants (n=17; mean age 64) completed a battery of cognitive tasks (CANTAB©) before beginning and after completing exercise training; control group participants (n=18; mean age 66) completed the battery on dates approximately 16-weeks apart. There were no significant differences between the groups on any cognitive performance measures based on ANOVA analyses (ps > 0.24). Due to the small sample size, we also calculated effect sizes. Effects of the exercise intervention were small for the total trial and total error outcomes on the paired associate learning task (d=0.20 and d=0.39, respectively), as well as for the spatial span task (d=0.38). For the control group, effect sizes were small for the verbal free recall task (d=0.23), medium for the rapid visual processing (d=0.62) and paired associate learning task (d=0.71 and
d=0.52 for the total trial and total error outcomes, respectively), and large for the spatial span task (d=1.02).

Much can be learned from the unexpected findings in both manuscripts. In Study 1, contrary to our a priori hypothesis, task-related brain activation increased with exercise training. This finding may suggest that exercise-induced cognitive reserve presents as increased neural capacity, rather than efficiency, in our sample. It is possible that our sample was not comparable to average older adults, and thus the women in our study did not employ the efficiency mechanism we expected based on previous research (Scarmeas et al., 2003). The average IQ of women undergoing fMRI was 119, which falls within the 90th percentile. These women also had been very socially and mentally active throughout life, according to their Lifetime Experience Questionnaire responses. High levels of ‘mental activity’-induced cognitive reserve at baseline may have affected how exercise-induced reserve manifested in these participants. It is also possible that exercise-induced cognitive reserve has completely different mechanisms than cognitive reserve ‘built’ through mental or social activity, and therefore our original hypothesis may have been misguided and this project fully exploratory. Alternatively, the findings do not fully support cognitive reserve theory because we found no evidence linking increased task-related brain activation with improved cognitive performance. The lack of a control group makes it even more difficult to determine whether the increased task-related brain activation was a true demonstration of beneficial, exercise-induced adaptations in the brain, or normal brain changes associated with aging or other factors.

In Study 2, we observed improvements on multiple cognitive tasks in control group participants. These unexpected effects may have resulted from a number of factors.
Less time between cognitive testing sessions in control compared to intervention participants may have meant that control participants felt more familiar with the cognitive battery at follow-up and may have been able to strategize more effectively. Additionally, control group participants were recruited to be part of a memory and thinking study (as opposed to an exercise study), and therefore may have been worried about memory. These participants may have been more motivated to improve their performance at their follow-up visit, and may have been more likely to engage in ‘brain training’ activities between sessions. Lastly, an experimenter bias may have negatively affected the performance of intervention participants at follow-up, as these participants became very familiar with the primary investigator over the course of the 16-week intervention and may have felt added pressure to improve their performance at follow-up.

Overall, Study 1 provides a stepping-stone for future cognitive reserve studies in the field of exercise science. Randomized, controlled investigations with more diverse samples should test our tentative conclusion that exercise-induced cognitive reserve presents as greater neural network capacity in healthy older women. Study 2 should also be replicated with a larger, randomized sample, and a careful eye toward avoiding practice effects, as investigations of the cognitive benefits of walking are timely and could make an important public health impact.
References


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Appendix A: McCausland Participant Screening Document

Participant ID: ____________

For Internal Use Only

MRI Participant Screening Document

HEIGHT ______ ft _______ in  WEIGHT _________ lbs  Date of Birth ____/____/______

1) Participant History
___ Yes ___ No  Have you ever done metal grinding, welding or machine shop work (job, hobby or student)?
___ Yes ___ No  Have you ever had metal removed from your eye(s) (including metal shavings, slivers, bullets)?
___ Yes ___ No  Are you pregnant or breastfeeding?
  (Date of last menstrual period? ___/___/_______)
___ Yes ___ No  Are you claustrophobic?
___ Yes ___ No  Do you experience vertigo or other vestibular abnormalities?

2) Participant History
___ Yes ___ No  Do you have sickle cell anemia?
___ Yes ___ No  Do you have a medical history of cancer?

3) Do you have any of the following in or on your body?
___ Yes ___ No  Cardiac wires or defibrillator
___ Yes ___ No  Medication Patch (Nicotine, Nitroglycerin)
___ Yes ___ No  Venous Filter, basket or stent
___ Yes ___ No  Dental Implants
___ Yes ___ No  Eye Implant
___ Yes ___ No  Bullets, BBs, Pellets, Metal Fragments of any kind
___ Yes ___ No  Implanted device (pain pump, bone stimulator, tissue expander)
___ Yes ___ No  Implanted Catheter
___ Yes ___ No  Penile Prosthesis
___ Yes ___ No  Fractured bones repaired with metal
___ Yes ___ No  Ear Implant
___ Yes ___ No  Joint Replacements
4) Do you have any of the following in or on your body?

___ Yes ___ No  Orthodontic Braces

___ Yes ___ No  Permanent Makeup (eyeliner, etc.) or Tattoo

Date of Tattoo: __________________________

Location of Tattoo Parlor: __________________________

5) Do you have any of the following in or on your body?

___ Yes ___ No  Artificial limbs

___ Yes ___ No  Removable dental work

___ Yes ___ No  Hearing aid (must be removed before entering scan room)

___ Yes ___ No  Body piercing jewelry

___ Yes ___ No  Medication patches (including nicotine)

6) List all past surgical procedures:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

7) List all allergies:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

The possible hazards of an MRI scan have been explained to me, and I understand that I can withdraw at this point for any reason, and that I do not have to disclose that reason to the experimenter.

Your signature below indicates that you understand this screening form and attest to its accuracy. If protocols require anonymous screening forms, then your signature on the Informed Consent Form will indicate compliance with this screening instrument.

Participant signature __________________________  Date ____________

Witness __________________________  Date ____________