COGNITIVE AND STRUCTURAL BRAIN CORRELATES OF PHYSICAL ACTIVITY AND FITNESS IN AGING: A CROSS-SECTIONAL VOXEL-BASED MORPHOMETRY STUDY

By

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To my parents and wonderful family

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The current study investigated whether fitness level or self-reported physical activity is a better predictor of gray matter volume in older adults (N=29). Given the scarcity of brain imaging studies reporting a direct relationship between cognitive and morphometric brain measures, the direct relationship between executive function and gray matter volume was also assessed using voxel-based morphometry (VBM). We further analyzed data from an independent physical activity intervention study (LIFE-P), conducted for 1-year in sedentary older adults, in an attempt to support our cross-sectional findings (N=20). It was found that fitness level, and not self-reported physical activity, displayed a protective role on gray matter volume as age increased, in regions typically affected by the aging process, such as the cerebellum bilaterally, fusiform/inferior lateral occipital cortex/lingual gyrus, and left hippocampus and parahippocampal gyrus. Executive functions did not directly predict gray matter volume in any area of the brain, nor did gray matter volume predict executive function performance above and beyond the contribution of age. Findings from the LIFE-P did not support our cross-sectional results and rather suggested that there was not a long-

term protective role of adherence to a physical activity regimen on the gray matter. Hence fitness level moderated the relationship between age and gray matter volume in areas previously reported to decline as a function of age, while self-reported physical activity levels failed to detect this finding. Future exercise intervention studies should rely on objective measures of fitness level (i.e., $VO2_{max}$) rather than on self-reported measures of physical activity.

CHAPTER 1
INTRODUCTION

Biological aging is characterized by declines in central nervous system integrity, function, and cognitive performance. The extant literature has reported an association between exercise, increased central nervous system integrity, and improved cognition in late-life. The overarching goal of this study is to examine the influence of self-reported physical activity level, fitness level, and cognitive performance on gray matter volume in older adults.

Age-Related Cognitive Decline

As age increases, individuals display slowed reaction times on tasks measuring memory search, lexical decision, mental rotation, speech discrimination, visual search, and digit-symbol substitution among others (Hofer & Alwin, 2008). Above and beyond decrements in speeded tasks, older adults display reductions in memory and reasoning beginning early in adulthood (Salthouse, 2001). Further, word retrieval (Obler & Albert, 1980) and verbal fluency decline in old age (Mayr & Kliegl, 2000), disrupting effective communications (Kempler & Zelinski, 1994). Nevertheless, age-related decrements in executive functions have been highlighted by many researchers as one of the core features of cognitive aging (Dempster, 1992; West, 1996). Executive functions can be defined as the mental processes controlling coordination, monitoring, inhibitory control, and task switching (Hofer & Alwin, 2008) which are differentially affected by biological aging (West, 1996).

Age-related cognitive decline has been identified as a risk factor for nursing home entry and the development of degenerative disease, such as Alzheimer's dementia (Statistics, 2006; Wilson, 2002). Therefore, developing interventions to mitigate age-

related cognitive decline and improve older adults' quality of life has become an important public heath goal. Exercise and physical activity level have been associated with improved cognitive function and positive emotional and physical health outcomes in older adults (Colcombe et al., 2003; McAuley, Shaffer, & Rudolph, 1995). Thus, exercise and increased physical activity levels may abate the deleterious effects of cognitive aging and merits further investigation.

Exercise and Cognition in Late-Life

The relationship between exercise and cognition has been studied for decades dating back to studies by Spirduso and colleagues who compared reaction time measures in younger and older adult sportsman to that of sedentary older adults. They found that simple and choice reaction time was faster in older adults who engaged in regular exercise when compared to their sedentary counterparts (Spirduso, 1975; Spirduso & Clifford, 1978). Since then, several research groups have continued to investigate the relationship between exercise and cognition in both cross-sectional and longitudinal samples.

Qualitative and quantitative reviews of the literature have postulated that late-life exercise results in cognitive benefits. Most reviews suggest that executive functions seem to be differentially benefited by exercise in older individuals (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004; Colcombe & Kramer, 2003; Hillman, Erickson, & Kramer, 2008; Kramer & Erickson, 2007; Kramer, Erickson, & Colcombe, 2006; McAuley, Kramer, & Colcombe, 2004), although general cognitive abilities profit as well. A meta-analysis of randomized-controlled trials of exercise revealed that regular involvement in exercise improves reaction time, spatial processing, controlled processes, and executive functions in older adults (Colcombe & Kramer, 2003). Further,

a longitudinal study reported that individuals with low baseline cardiorespiratory fitness (CRF) scores displayed greater decrease in global cognition over six years, while cognitive performance remained stable for those whose CRF was higher at baseline (Barnes, Yaffe, Satariano, & Tager, 2003). Similarly, exercise intervention studies have reported that even low-intensity physical activity and aerobic exercise improve episodic memory (Ruscheweyh et al., in press) and executive functions respectively (Colcombe, Kramer, Erickson et al., 2004). Thus, several research studies have identified a positive relationship between exercise and cognitive improvements in late-life.

Exercise and Brain Function in Late-Life

Functional magnetic resonance imaging (fMRI) studies have also uncovered changes in older adults' functional brain activity following exercise interventions. Colcombe and colleagues (2004) measured older adults' performance on a modified Flanker task using fMRI before and after a six month (walking) intervention. The authors found that older adults in the exercise group showed faster reaction times and increased accuracy on the Flanker task when compared to those in the control group (stretching and toning). These changes in cognitive function were accompanied by concomitant brain activity changes in attentional networks, suggesting that those who exercised displayed improved capacity to allocate attentional resources during the Flanker task (Colcombe, Kramer, Erickson et al., 2004). Similarly, long-term engagement in physical activity has been shown beneficial for brain activity and psychomotor speed even two years after termination of a physical activity intervention in older adults (Rosano et al., 2010). Further, studies have reported that the functional brain connectivity of structures usually associated with attentional processes (posterior cingulate cortex and middle frontal gyrus), is a significant source of variance in the

relationship between aerobic fitness and executive functions, and could thus be considered a plausible underlying mechanism of the exercise-induced cognitive benefits observed in late-life (Voss et al., 2010). Similarly, following a four-month exercise intervention, Burdette and colleagues found heightened connectivity of the hippocampus to the anterior cingulate cortex, as well as increased cerebral blood flow to the hippocampus only in older adults assigned to an exercise group (Burdette et al., 2010). These functional brain imaging findings further support the potential of exercise to increase plasticity in late-life by exerting changes at the neural level.

Exercise and Brain Structure in Late-Life

Nevertheless, exercise has not only been associated with improved cognition and changes in functional brain activity and connectivity, but also with increases in gray and white matter brain volumes in late-life. With age, older adults display reductions in gray and white matter volumes (Good et al., 2001; Raz & Rodrigue, 2006; Tisserand et al., 2004). The most pronounced reductions in gray matter occur in prefrontal, temporal, and parietal cortices (Raz & Rodrigue, 2006; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Tisserand et al., 2004), while changes in white matter microstructure suggest that the anterior white matter is differentially affected by age (Raz & Rodrigue, 2006).

In order to measure the relationship between exercise and brain volume, some investigators have conducted structural brain studies in older adults who are aerobically fit or sedentary or who become aerobically fit following an exercise intervention. Colcombe and colleagues, in a cross-sectional study, predicted that brain areas most affected by aging (frontal, temporal, and parietal lobes) would be spared of atrophy in older adults who display high aerobic fitness levels. The authors found that, indeed,

older adults with higher fitness levels, displayed greater gray matter volumes in prefrontal, temporal, and superior parietal cortex, as measured by voxel-based morphometry (VBM), than those with lower fitness scores (Colcombe et al., 2003). Further, they found that the anterior corpus callosum, which is critical for inter-hemispheric communication, was spared in older adults with higher fitness levels. The same findings were supported following a six-month exercise intervention in which the aerobic training group displayed increased gray matter volumes in frontal and temporal brain regions, as well as increased white matter volumes in the anterior corpus callosum (Colcombe et al., 2006). Other cross-sectional studies have reported associations between aerobic fitness, hippocampal volume, and spatial memory (Erickson et al., 2009). Longitudinal studies have supported the cross-sectional literature indicating that physical activity at baseline predicts higher gray matter volume over nine years (Erickson et al., 2010). Furthermore, exercise intervention studies have found positive effects of exercise on gray matter volume and cognitive function in older adults (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., in press).

Given that gray matter volumes have been associated with improved cognitive function in older adults, investigators have suggested that exercise-induced neural changes may be the underlying mechanism by which exercise improves cognitive function (Colcombe et al., 2006; Colcombe, Kramer, Erickson et al., 2004; Erickson et al., 2009; Erickson et al., 2011). Animal studies have confirmed human findings by demonstrating improved water maze performance in rats and mice following exercise. These cognitive changes are accompanied by increases in angiogenesis, synaptogenesis, neurogenesis, and neurotrophic factors related to central nervous

system plasticity, such as brain-derived neurotrophic factor [BDNF] (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005; Pereira et al., 2007; Swain et al., 2003; Vaynman & Gomez-Pinilla, 2005; Vaynman, Ying, & Gomez-Pinilla, 2004).

Since older adults display deficits in executive functioning, and the frontal lobes are involved in these functions, increased cortical frontal volumes should result in improved executive abilities. Most structural brain studies of exercise in aging have not collected cognitive performance measures (Colcombe et al., 2003; Colcombe et al., 2006) or have simply described them in parallel to brain structure, without directly correlating brain volume differences with cognitive performance (Gordon et al., 2008). For example, Gordon and colleagues (2008) conducted a cross-sectional study of brain structure and cognitive aging which aimed at further describing the relationship between aging, cardiopulmonary fitness, and education levels. They collected several neuropsychological measures; however, these measures were correlated to fitness and education levels separately and their association with brain structure was not directly assessed. Thus defining the relationship between gray matter volume and cognitive performance in older adults remains understudied.

Similarly, the type and intensity of exercise or physical activity needed to achieve neural and cognitive benefits is not well-characterized in the literature. In an effort to better understand these differences, Ruscheweyh and colleagues (in press) investigated the intensity of exercise needed for observable cognitive effects in older adults. The authors studied the influence of different physical activity regimens on episodic memory function, gray matter volume, and neurotrophin levels. They found that physical activity as a whole (low-intensity aerobic, medium-intensity aerobic, and

physical activity embedded within activities of daily living) can confer beneficial cognitive effects. On the other hand, one study suggested that levels of physical activity, and not cardiovascular fitness, were associated with improved memory performance, and physical activity was also related to higher gray matter volume in prefrontal and cingulate cortex (Flöel et al., 2010).

In sum, both cross-sectional and exercise intervention studies have identified a strong link between aerobic fitness, physical activity and improved cognitive function in older adults. These changes in cognitive function seem to be supported by preservation or increases in gray and white matter volumes in areas critical for higher-order cognitive functioning such as the frontal, temporal, and parietal cortex.

The Present Study

The purpose of the present study is to better characterize the differential effects of self-reported physical activity and fitness level on gray matter volume and cognitive performance in older adults. For this purpose, we collected structural magnetic resonance images (MRI) in a sample of neurologically healthy older adults in order to conduct voxel-based morphometry (VBM) analyses. We also obtained executive function performance measures on the same sample to evaluate the relationship between fitness, physical activity, brain volume and cognitive function. In addition, this study used cognitive and structural brain data from an independent exercise intervention study in an attempt to add converging evidence to our cross-sectional findings. For this purpose, cognitive and structural brain MRI data from the Lifestyle Interventions and Independence for Elders pilot study (LIFE-P) was analyzed (Pahor et al., 2006).

CHAPTER 2
AIMS & HYPOTHESES

Aim 1

To investigate the unique relationship between fitness levels, age, executive function, and gray matter volume in older adults, as well as the moderating role of fitness in the relationship between age and gray matter volume.

Hypothesis 1

Fitness and executive function performance will add unique variance to the prediction of gray matter volumes, with higher fitness and higher executive functions associated with higher gray matter volumes. Age, however, will be negatively correlated to gray matter, especially within the prefrontal, temporal, and parietal cortex. Further, fitness level will moderate the relationship between age and gray matter volume.

Aim 2

To investigate the unique relationship between self-reported physical activity levels, age, executive function, and gray matter volume in older adults, as well as the moderating role of physical activity in the relationship between age and gray matter volume.

Hypothesis 2

Self-reported physical activity levels and executive function performance will add unique variance to the prediction of gray matter volumes, with higher physical activity levels and higher executive functions associated with higher gray matter volumes. Age, on the other hand, will display negative associations with gray matter volume, especially in areas typically affected by biological aging such as prefrontal, temporal, and parietal

cortex. Physical activity will moderate the relationship between gray matter volume and age based on findings from the literature.

Aim 3

To examine whether gray matter volume predicts executive function performance above and beyond fitness/physical activity and age.

Hypothesis 3

Gray matter volume will predict executive function performance above and beyond the contribution of fitness/physical activity and age.

Aim 4

To use the LIFE-P data to compare the cognitive and gray matter volume differences between participants assigned to the Physical Activity (PA) group and those assigned to the Successful Aging control group (SA) two years after termination of the physical activity intervention.

Hypothesis 4

Participants from the LIFE-P study who were previously assigned to the Physical Activity (PA) group will display higher gray matter volumes than those assigned to the Successful Aging control group (SA), especially within areas vulnerable to biological brain aging (frontal, temporal, parietal cortex). Participants in the PA group will also display better performance on a task of executive function when compared to the SA group.

CHAPTER 3
CROSS-SECTIONAL STUDY DATA

Methods

Participants

Three groups of participants were originally collected as part of a larger study: physically active older adults, sedentary older adults, and a young adult group. For the purposes of the current study, and given the overlap of physical activity and fitness measures between the physically active and sedentary older groups, we utilized the data from older adults only, with physical activity and fitness as continuous variables. The original physically active group consisted of 16 neurologically healthy older adults (ages 60-85) who self-reportedly performed voluntary aerobic exercise lasting at least 30 minutes for a minimum of 3 times per week. The original sedentary older adult group was matched for age to the physically active group, and was comprised of 13 neurologically healthy older adults, ages 61-81, who by self-report, performed aerobic exercise less than 45 minutes per week. Data from 15 healthy young adults (ages 18-30) was also collected, but it is not included in the present study. Thus the total sample size for the current study is 29 older adults. All participants were healthy community-dwelling older adults recruited from the general Gainesville, FL area. Signed informed consent was obtained from all participants according to guidelines established by the Health Science Center's Institutional Review Board at the University of Florida. Participants were compensated for their participation in the study. See Table 3-1 for participant demographics.

Exclusion Criteria

All participants were right-handed, native English speakers, who were deemed eligible for MRI scanning following an extensive screening protocol (e.g., no cardiac pacemaker, ferrous metal implants, or claustrophobia). Participants were free of a history of diagnosable neurological conditions (i.e., stroke, Alzheimer's disease, Parkinson's disease, mild cognitive impairment), history of head trauma with loss of consciousness, cardiac conditions, learning disabilities, attention deficit disorder, history of alcohol or drug abuse (for at least six months prior to participation), and psychiatric conditions. Older adults currently prescribed beta-blockers for hypertension management were not included in the study. On neuropsychological testing, all subjects obtained Mini-Mental State Examination (MMSE) scores ≥ 27 (Folstein, Folstein, & McHugh, 1975) indicating no global cognitive impairment.

Aerobic Fitness and Physical Activity Assessment

A modified Cooper treadmill test was conducted (Cooper, 1968) in which participants were asked to cover as much ground as possible by walking, jogging, or running on a treadmill for twelve minutes. Distance traveled in twelve minutes (self-paced, variable speed) was the main fitness outcome measure. To measure self-reported physical activity level, we used a modified version of the Leisure-Time Exercise Questionnaire (LTEQ), which is a three-item scale that asks participants to rate how often they engaged in mild, moderate, and strenuous leisure-time exercise (Godin, Jobin, & Bouillon, 1986; Godin & Shephard, 1985). The LTEQ is a reliable and valid measure of leisure-time exercise behavior in adults (Jacobs, Ainsworth, Hartman, & Leon, 1993) that allows for calculation of total number of minutes spent in moderate and strenuous physical activity, which was modified in the present study to obtain total

minutes of moderate and strenuous physical activity performed in one week. Hence, distance travelled during the treadmill test was considered a measure of fitness level, while minutes spent performing moderate and strenuous physical activity, as measured by the modified-LTEQ, assessed subjective physical activity level.

Neuropsychological Assessment

Each participant completed approximately two hours of neuropsychological testing for the larger study. For the purposes of this study, we created an executive function composite score for each participant given the reported declines in executive function that occur as a function of age, as well as the beneficial effects that exercise has been suggested to exert on measures of executive function in older adults. The executive function composite score was comprised of the averaged total scores for the following measures: letter fluency total correct (FAS), number correct on a reasoning measure (Letter Series*), Trails B score, reaction time (RT) during a modified version of the Flanker Task*, Lexical Decision task* RT, and Number Copy and Symbol Digit* RT. Measures marked with an asterisk (*) were computerized for ease of administration and to obtain RT measures as well as accuracy. Computerized measures were programmed using DirectRT v2004 and MediaLab experimental research software (Jarvis, 2004a, 2004b). All cognitive variables were analyzed using PASW statistics 18, Release version 18.0.0 (PASW/SPSS, 2009).

Structural Imaging

Structural MRI images were acquired on a 3 Tesla Achieva whole-body scanner (Philips), with an 8-channel SENSE radio frequency head coil, at the McKnight Brain Institute of the University of Florida. For the VBM analyses, structural TFE T1-weighted images were acquired for 160x1mm sagittal slices (FOV=240mm; TE=3.685 ms;

TR=8.057 ms; FA=8 degrees; matrix=256x256, voxel size=1.0mm x 0.938mm x 0.938mm).

Procedure

An exercise screening questionnaire and an MRI screen were conducted via telephone to identify potential study candidates. For the larger study, older adults who reportedly performed voluntary aerobic exercise lasting at least 30 minutes for a minimum of 3 times per week were temporarily assigned to the physically active group. Those older adults who reportedly performed aerobic exercise less than 45 minutes per week were temporarily assigned to the sedentary older adult group. Given the nature of the current study, we did not analyze data by the assigned groups, but rather used fitness and physical activity as continuous variables. Older adults who qualified for the study based on the MRI and exercise phone screens, were asked to obtain written clearance from their primary care physician in order to participate in the treadmill test. Once physician's clearance was in place, participants were scheduled for the first study session. During the first session, which lasted approximately 2.5 hours, participants underwent neuropsychological testing first (2 hours), followed by the aerobic fitness treadmill test (12 minutes). Heart rate was monitored throughout the treadmill assessment. Participants were then instructed on how to answer the modified LTEQ, which they completed for a monitoring period of seven days following the first session. Structural imaging scans were obtained during the second session, which was scheduled following the seven day monitoring period. At this time, participants brought the completed LTEQ to assess self-reported physical activity levels.

Data Analyses

Structural Imaging

Image preprocessing

MRI structural images were analyzed using FSL-VBM, a voxel-based morphometry (VBM) style analysis (Ashburner & Friston, 2000; Good et al., 2001), carried out with FMRIB Software Library (FSL) version 4.1 tools (Smith et al., 2004). This technique allows for the identification of different types of brain tissue (i.e., gray matter, white matter, and cerebrospinal fluid or CSF) at the voxel level by calculating the probability that each voxel contains a particular tissue-type.

Pre-processing of the structural images for VBM analysis consisted of the following steps: a) removing the skull and other non-brain tissue from the structural images using flsvbm_1_bet (Smith, 2002), b) performing tissue-type segmentation to generate partial gray matter volumes for each participant in the native space using FAST4 (Zhang, Brady, & Smith, 2001), c) aligning the resulting gray matter partial volumes to MNI152 standard space using the non-linear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The resulting images were concatenated and averaged to create a study-specific template containing the registered gray matter images for each of the 29 older adult subjects (fslvbm_2_template -n). All of the gray matter images were then non-linearly registered to the study-specific template (fslvbm_3_proc). To account for changes in voxel size that occur within the image registration process (expansion and contraction), all registered partial volume images were modulated by dividing by the Jacobian of the warp field (fslvbm_3_proc). The modulated, segmented images were then smoothed

with an isotropic Gaussian kernel of sigma 2mm, which corresponds to 4.6mm full-width half-max (FWHM).

Image analyses: regression models

All predictor variables entered into the model were first normalized using the Blom transform method available on PASW statistics 18, Release version 18.0.0 (PASW/SPSS, 2009) software to meet GLM assumptions. Fitness level and executive functions composite were orthogonalized (removed shared variance) due to their significant correlations with age (fitness r= -.40, p=.03; executive r= -.47, p=.01) to avoid problems resulting from multicollinearity (Pedhazur, 1997). For this purpose, a simple regression model with fitness as the dependent variable and age as the predictor was conducted while saving the unstandardized residuals. This procedure results in a residualized fitness variable ($\text{fitness}_{\text{-age}}$) from which the shared variance between age and fitness has been removed and represents the unique variance associated with fitness level. The same procedure was followed for the executive function composite, deriving an executive composite variable that is independent of age ($\text{executive}_{\text{-age}}$). Subsequently, age, physical activity, and the interaction terms were centered (mean of 0) as required for FSL tools to carry out multiple regression analyses.

We used the randomize option in FSL, which is a permutation-based program allowing for modeling and inference testing using standard general linear model design, when the null distribution of a statistic map is unknown. To describe the unique relationship between gray matter, fitness level, physical activity level, and cognitive function, we conducted two voxel-wise multiple regression models under the general linear model, higher level/non-time series design option in FSL. The first regression model used voxel-wise gray matter volume as the dependent variable, and $\text{fitness}_{\text{-age}}$

(distance travelled in 12 minutes during treadmill test), age, executive$_{-age}$ function composite, and the interaction between age and fitness$_{-age}$ (age X fitness$_{-age}$) as predictors. The second regression model included voxel-wise gray matter volume as the dependent variable and physical activity (self-reported minutes of moderate + strenuous activity in one week), age, executive$_{-age}$ function composite, and the interaction between age and physical activity (age X pa) as predictors. The resulting probability maps were corrected for family-wise error (p<.05) using the Threshold-Free Cluster Enhancement (TFCE) method implemented on FSL. This method enhances cluster-like regions more than background (noise) by creating output that is a weighted sum of all of the local clustered signal, without the need for arbitrary cluster thresholding (Smith & Nichols, 2009). To obtain parameter estimates as indicators of effect size, regardless of significance level, we performed another set of ordinary least squares regressions based on the same models described above using FSL FEAT. The resulting statistic maps provided unstandardized b-weights (b) for each of the predictors entered into the model. Each b-weight statistic map was transformed to standardized beta-weights (β) using fslmaths based on the following formula: β = b*(standard deviation of the independent variable/standard deviation of the dependent variable).

Neuropsychological Data

Given the neuropsychological data's departure from normality, all cognitive variables were normalized using the Blom transform method available within PASW statistics 18, Release version 18.0.0 (PASW/SPSS, 2009). After normalization, all RT measures were reflected so that higher values represent better performance. Then, the Blom-transformed scores of all cognitive measures of executive function (as described in the methods section) were averaged to create the executive function composite score

for each participant, which was entered into the regression analyses as a predictor of gray matter volume on each of the two regression models carried out on FSL.

To examine whether gray matter volume predicted executive function performance above and beyond the contribution of fitness or physical activity and age, hierarchical regression models were carried out on PASW statistics using mean gray matter volumes extracted from specific regions of interest (see results section).

Results

Fitness Regression in FSL

Fitness$_{-age}$, age, and executive$_{-age}$ function did not significantly predict gray matter volume in any brain region after correcting for multiple comparisons (TFCE $p<.05$). The interaction between age and fitness$_{-age}$, however, survived family-wise correction at the $p<.05$ level. Areas that survived family wise error correction include: left and right cerebellum, left hippocampus and parahippocampal gyrus, and right and left inferior lateral occipital cortex/occipital fusiform, and left lingual gyrus. See Figure 3-1 for a depiction of the brain regions in which the interaction between age and fitness$_{-age}$ predicted gray matter volume.

Fitness Regressions in PASW

To decompose the significant interaction and better understand the relationship between age, fitness and gray matter volume in these regions, a mask of the significant areas was created and separated into the five distinct anatomical regions it comprised (left cerebellum, right cerebellum, left hippocampus/parahippocampal gyrus, right occipital fusiform/inferior lateral occipital cortex, left occipital fusiform/inferior lateral occipital cortex/lingual gyrus). Then, the average gray matter volume and median βs were extracted from these regions and exported from FSL to be analyzed with PASW

software. Multiple regression models with fitness$_{-age}$, age, executive$_{-age}$ function, and age X fitness$_{-age}$ predicting gray matter volume at each of the five ROIs were computed. The fitness$_{-age}$ variable was dichotomized (see Table 3-2 for participant characteristics per fitness group) using a median split in order to visually plot the interactions between fitness, age, and gray matter volume at each of these regions. See Figure 3-3 for scatter plots depicting the interaction between age and fitness$_{-age}$ level on gray matter volume at each of the ROIs.

For the left cerebellum (Lcer), the regression model was significant, $F(4,24)=9.4$, $p<.001$, *Adj* $R^2=.55$. The interaction between age and fitness$_{-age}$ was significantly associated with gray matter volume, where participants with lower fitness levels did not show the beneficial effects of fitness on gray matter volume as age increased: age X fitness $t(24)=5.82$, $p<.001$, $\beta=.76$. Within the right cerebellum (Rcer), the overall model was significant $F(4,24)=7.78$, $p<.001$, *Adj* $R^2=.49$. Fitness level significantly moderated the relationship between age and gray matter volume, where higher fitness level had a higher impact on gray matter volume with increasing age: age X fitness $t(24)=5.42$, $p<.001$, $\beta=.75$. The regression model was significant for the left hippocampus/parahippocampal gyrus (Lhippo) as well $F(4,24)=11.91$, $p<.001$, *Adj* $R^2=.61$. Fitness$_{-age}$, age, and the interaction between age and fitness$_{-age}$ level were significantly associated with gray matter volume. Here, those individuals with lower fitness scores did not display the mitigating effect of fitness on gray matter volumes as age increased when compared to those with higher fitness levels; fitness $t(24)=-3.14$, $p<.01$, $\beta=-.38$; age $t(24)=-3.77$, $p<.01$, $\beta=-.45$; age X fitness $t(24)=5.58$, $p<.001$, $\beta=.67$. For the right occipital fusiform/inferior lateral occipital cortex ROI (RLOC), the

regression model was significant $F(4,24)=10.69$, $p<.001$, $Adj\ R^2=.58$. Fitness$_{-age}$ level and the age X fitness$_{-age}$ interaction were significantly associated with gray matter volume in this area, where those with higher fitness scores showed increased impact of fitness on gray matter volume as age increased: fitness $t(24)=-2.71$, $p<.05$, $\beta=-.34$; age X fitness $t(24)=6.38$, $p<.001$, $\beta=.80$. Finally, for the left occipital fusiform/inferior lateral occipital cortex/lingual gyrus (LLOC) ROI, the regression model was significant $F(4,24)=13.67$, $p<.001$, $Adj\ R^2=.64$. Fitness$_{-age}$, age, and age X fitness$_{-age}$ were significantly correlated to gray matter volume in this region, in which those with lower fitness scores did not display a protective effect of fitness on gray matter as age increased: fitness $t(24)=-2.56$, $p<.05$, $\beta=-.30$; age $t(24)=-3.94$, $p<.01$, $\beta=-.45$; age X fitness $t(24)=6.25$, $p<.001$, $\beta=.72$. Refer to Figure 6-1a for a graphed representation of the median βs at each of the ROIs. The positive slope of the relationship between age and gray matter volume in the Rcer and RLOC within the high fitness group was not due to the older individuals in this group being more educated than those in the low fitness group, since age was not significantly correlated to education within the high ($r=-.16$, $p=.60$) or low fitness groups ($r=.20$, $p=.49$).

Physical Activity Regression in FSL

Physical activity, age, executive function$_{-age}$, and the interaction between age and physical activity did not significantly predict gray matter volume after correcting for multiple comparisons (TFCE $p<.05$).

Direct Comparison between Fitness$_{-age}$ & Physical Activity in FSL

Based on the above results, it would appear that the age X fitness$_{-age}$ interaction is a better predictor of gray matter volume than self-reported physical activity or its associated interaction with age. However, a head-to-head comparison of these

potential predictors is necessary to make such a statement definitively. To confirm if the age X fitness$_{\text{-age}}$ interaction was a better predictor of gray matter volume than physical activity level, a different whole-brain multiple regression model was conducted on FSL with fitness$_{\text{-age}}$, physical activity, age X fitness$_{\text{-age}}$, and age X physical activity as predictors of voxel-wise gray matter volume. Results indicated that the interaction between age and fitness$_{\text{-age}}$ was the only significant predictor of gray matter volume (TFCE p<.05). The areas in which fitness moderated the relationship between age and gray matter volume in the current analysis were much smaller than, but encompassed by the same anatomical regions as the significant areas in which the age X fitness$_{\text{-age}}$ interaction predicted gray matter volume in the previous regression analysis (refer to Fitness Regression in FSL section). None of the other potential predictor variables (fitness$_{\text{-age}}$ alone, physical activity alone, age X fitness$_{\text{-age}}$, age X physical activity) predicted gray matter volume in any brain regions after correcting for multiple comparisons (TFCE p<.05). Thus, the interaction between age and fitness$_{\text{-age}}$ was a better predictor of gray matter volume than physical activity level or its associated interaction with age in a head-to-head comparison. See Figure 3-2 for the overlap of significant regions between the two regression models.

Neuropsychological Data

Two regression models were conducted to predict executive function in the current sample. The first was a hierarchical regression model in which the executive function composite was the dependent variable. The predictors were entered in the following order: block 1=fitness$_{\text{-age}}$; block 2=age; block 3=age X fitness$_{\text{-age}}$; and block 4= mean gray matter volume for the average of the five ROIs (Lcer, Rcer, Lhippo, RLOC, LLOC). Fitness$_{\text{-age}}$ alone did not significantly predict executive function, $F(1,27)=.12$, $p=.73$,

R^2=.005, Adj R^2=-.032. Adding age to the model significantly increased variance explained by 22% (p=.012) above and beyond that explained by fitness$_{-age}$ alone, F(2,26)=3.71, p<.05, R^2=.22, Adj R^2=.16. When adding the interaction term between age and fitness$_{-age}$ into the model, there is a significant increase in variance explained by 12% (p=.042), F(3,25)=4.34, p<.05, R^2=.34, Adj R^2=.26. The addition of gray matter volume to the model did not significantly contribute additional variance in executive function scores, F(4,24)=3.13, p<.05, R^2=.34, Adj R^2=.23, R^2 change=0%, p=.92 . Coefficients for the last model indicate that age is the only predictor that contributes uniquely to the total variance in executive functions; fitness$_{-age}$ t(24)=-.76, p=.46, β=-.15; age t(24)=-2.72, p<.05, β=-.49. age X fitness$_{-age}$ t(24)=1.18, p=.25, β=.38; mean gray matter volume t(24)=-.11, p=.92, β=-.04.

The second hierarchical regression model included the following predictors of executive function: block 1=physical activity; block 2=age; block 3=age X physical activity; and block 4= mean gray matter volume for the average of the five ROIs. Physical activity alone did not predict executive function, F(1,27)=1.85, p=.19, R^2=.064, Adj R^2=.029. Adding age to the model contributed 23% additional variance (p<.01), F(2,26)=5.52, p<.05, R^2=.30, Adj R^2=.24. The addition of the age X physical activity interaction did not contribute additional variance (R^2change=0%, p=.92) to the model, F(3,25)=3.54, p<.05, R^2=.30, Adj R^2=.21. Similarly, gray matter volume did not significantly explain any additional variance (R^2change=4%, p=.25) on executive function scores, F(4,24)=3.06, p<.05, R^2=.34, Adj R^2=.23. Coefficients for the last model indicate that only age contributes uniquely to the total variance in executive functions; physical activity t(24)=-1.10, p=.29, β=-.2; age t(24)=-2.47, p<.05, β=-.43; age X pa

$t(24)=-.28$, $p=.79$, $\beta=-.05$; mean gray matter volume $t(24)=1.19$, $p=.25$, $\beta=.22$. See Appendix for a graphed representation of median βs by ROI (Figure 6-1b).

Discussion

It has been consistently shown in the literature that biological aging is accompanied by neural challenges and concomitant declines in cognitive performance. Several studies have suggested that exercise and increased physical activity in older adults can help mitigate the effects of biological brain aging, thus delaying or preventing cognitive decline. There are discrepancies in the literature regarding the differential contribution of aerobic fitness and physical activity to the preservation of brain tissue and cognitive performance in late-life. Moreover, many studies assessing the relationship between brain volume and fitness levels have not measured the direct and unique relationship between cognitive function and brain volume, but rather assess it indirectly or not at all (Colcombe et al., 2003; Colcombe et al., 2006; Gordon et al., 2008). The main purpose of the current study was to evaluate whether fitness and/or physical activity better predict gray matter volume and if they moderate the relationship between age and gray matter volume, while also assessing the direct relationship between brain volume and executive function in older adults.

We found that the interaction between fitness level and age predicted gray matter volume in bilateral occipital and cerebellar regions, as well as in the left hippocampus, while self-reported physical activity level did not predict gray matter volume in any brain region in this sample. Thus, the interaction between age and fitness level was a better predictor of gray matter volume than self-reported physical activity level in the current sample. This finding is not surprising given the self-report nature of the physical activity variable, which is confounded by participants accurately assessing and recalling the

type and frequency of activities they have performed daily, for seven days. Further, this self assessment was a snap-shot of only one week, which may not have been representative of most weeks for all participants. Our measure of fitness, on the other hand, was an objective measure of distance travelled on a treadmill over a 12 minute period and it was a modification of a well-established method to derive aerobic fitness levels (Cooper, 1968). Although this fitness measure is not optimal, and assessing maximal oxygen consumption ($VO2_{max}$) would have been preferred, we were able to find that fitness level significantly moderated the relationship between gray matter volume and aging in five distinct brain regions: the left cerebellum, right cerebellum, right occipital fusiform/inferior lateral occipital cortex, the left hippocampus and parahippocampal gyrus, and the left occipital fusiform/inferior lateral occipital cortex/lingual gyrus. The hippocampus, cerebellum, and occipital cortices have been shown to decline as a function of age. The hippocampus has been shown to shrink at a medium rate of 1.23% each year. Similarly, the median correlation of brain volume with age in the cerebellum is r=-.30, and in occipital cortex is estimated at r=-0.19, (Raz & Rodrigue, 2006). Thus, it is not surprising that higher fitness levels would help mitigate the effects of age on brain volume in these regions. Moreover, positive associations between fitness level and brain volume in these regions have been previously reported in the literature (Erickson et al., 2009; Erickson et al., 2010; Erickson et al., 2011; Honea et al., 2009). However, we were unable to find associations between fitness and gray matter volume in frontal, lateral temporal, and parietal cortices as previously reported in the literature (Colcombe et al., 2003; Colcombe et al., 2006; Erickson et al., 2010; Flöel et al., 2010; Ruscheweyh et al., in press). Given that these regions are

amongst the first ones to be affected by aging, and fitness level has been shown to reduce tissue brain loss in the same areas (Colcombe et al., 2003; Colcombe et al., 2006), it is unclear why we were unable to find such associations in the current sample. Previous studies do not report whether they orthogonalized their predictor variables before entering them into the regression analyses (Colcombe, 2003). If fitness level is not made independent from age in a regression analysis, it is possible that the shared variance between age and fitness might explain most of the variance associated with gray matter volume in the frontal and temporal lobes. This could potentially explain why we obtained significant results in occipital rather than frontal brain regions, given that our fitness variable was independent from age and represented the unique effect of fitness on gray matter volume rather than the shared effect of fitness and age on gray matter volume. Furthermore, given that our measure of fitness is different from those usually reported in the literature (i.e. $VO2_{max}$ or estimates thereof), the current study may have captured variance associated with a different aspect of fitness level that does not overlap completely with measures such as $VO2_{max}$ (which assesses cardiac output). Another likely explanation for the current findings is that power to detect significant differences was affected given our small sample size (N=29). The same can be said regarding the lack of contribution of the executive composite measure to predicting gray matter volume, as well as the lack of contribution of gray matter volume as a unique predictor of executive function. First, the small sample size makes it difficult to find significant associations. Second, the executive function composite used in the current study differs from the typical measures reported in the VBM and exercise literature (i.e., spatial, episodic, and verbal memory, intelligence tests). Similarly, some of the tests

included in the executive function composite (i.e., number copy and symbol digit) may be considered a measure of psychomotor speed rather than executive functions by some investigators, possibly extending the interpretation of the composite variable to an area other than executive function. This circumstance is further complicated by the fact that detecting associations between brain volume and cognitive measures has proven difficult in the literature due to participant's individual differences in prodromal disease states, the nature of the measures used to assess cognitive function, and the composition of the sample (Raz, 2000; Raz & Rodrigue, 2006).

In sum, fitness level moderated the relationship between gray matter volume and age such that the impact of fitness level became more important as age increased. Given that gray matter volume decreases with age, it should be expected that the impact of fitness level becomes more important as age increases and neural challenges become more apparent. Hence, remaining fit in late-life seems more impactful to neuroplasticity once neural challenges, such as gray matter volume loss, have taken place. The current findings attest to the neuroprotective role that fitness plays in late-life, by sparing gray matter volume loss as age increases.

Executive function performance was not a significant predictor of gray matter volume in the current study and gray matter volume did not predict executive function performance above and beyond the contributions of age. Future research investigating the relationship between fitness, physical activity, cognitive function, and brain volume should be longitudinal/interventional in nature and measure physical activity and fitness levels utilizing objective variables rather than self-report measures. Similarly, cognitive performance should be measured consistently between studies to reduce

methodological variability and increase scientific comparability. Furthermore, future research should report on the correlation between predictor variables (i.e. fitness, age, cognitive measures) to better understand the unique contributions of each variable to gray matter volume.

3-1 Cross-sectional study participant characteristics

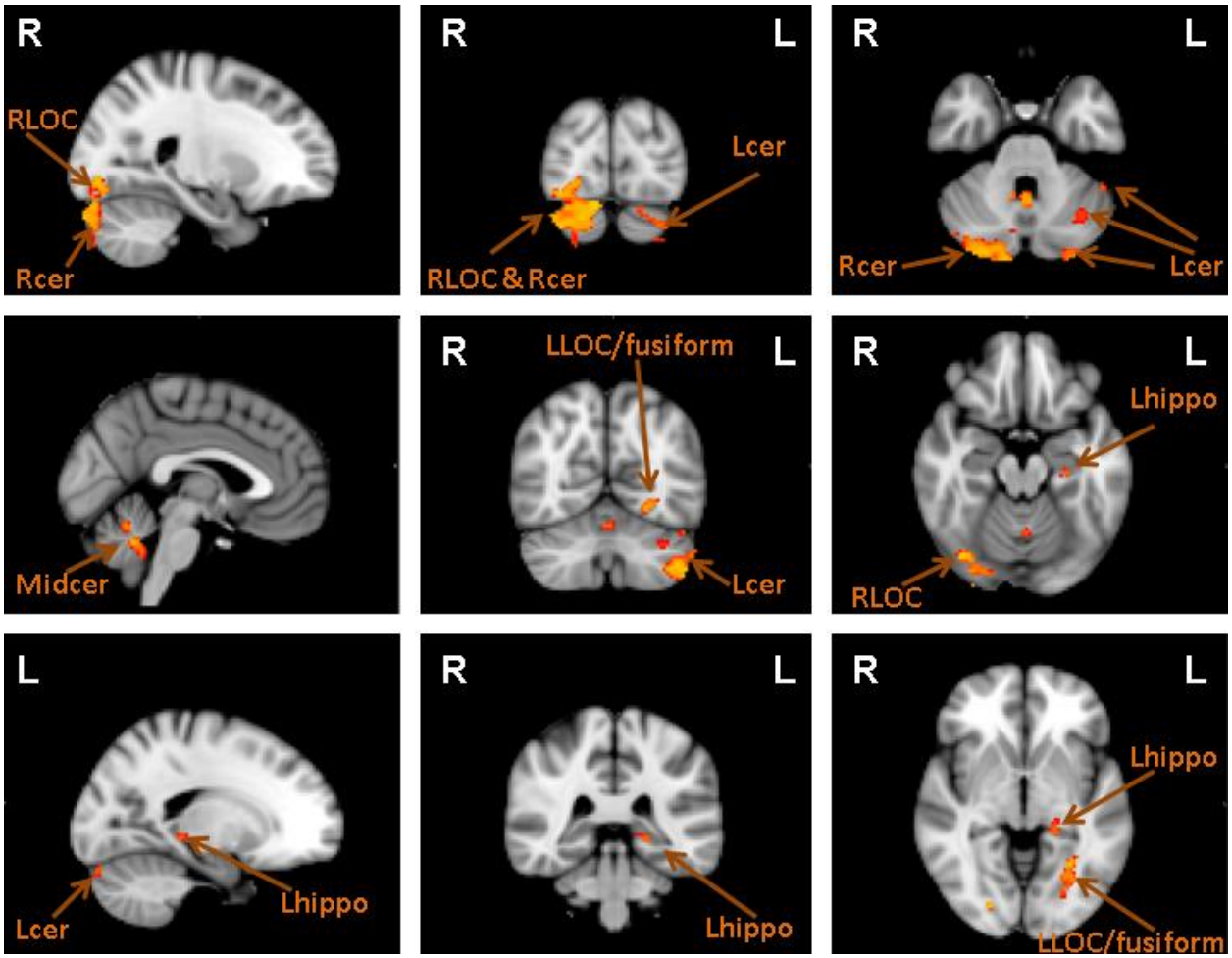
	Mean	SD	Minimum	Maximum
Age	68.38	5.98	60.00	85.00
Education	16.14	2.36	12.00	20.00
Gender		18 female / 11 male		
PA	242.86	204.78	0.00	900.00
Fitness	0.55	0.21	0.19	1.01
MMSE	28.97	0.98	27.00	30.00
Executive	0.00	0.69	-1.19	1.14
Lcer	0.61	0.12	0.38	0.81
Rcer	0.59	0.12	0.34	0.84
Lhippo	0.35	0.07	0.22	0.50
RLOC	0.66	0.14	0.44	0.98
LLOC	0.65	0.15	0.39	0.96

Notes: SD = standard deviation; PA = physical activity variable; MMSE = Mini Mental State Examination; Executive = Blom-transformed executive function composite; the remaining variables depict the mean gray matter volume for each of the following regions of interest (ROI): Lcer = left cerebellum; Rcer = right cerebellum; Lhippo = left hippocampus/parahippocampal gyrus; RLOC = right inferior lateral occipital cortex/occipital fusiform gyrus; LLOC = left inferior lateral occipital cortex/occipital fusiform gyrus/lingual gyrus.

3-2 Cross-sectional study participant characteristics by median split

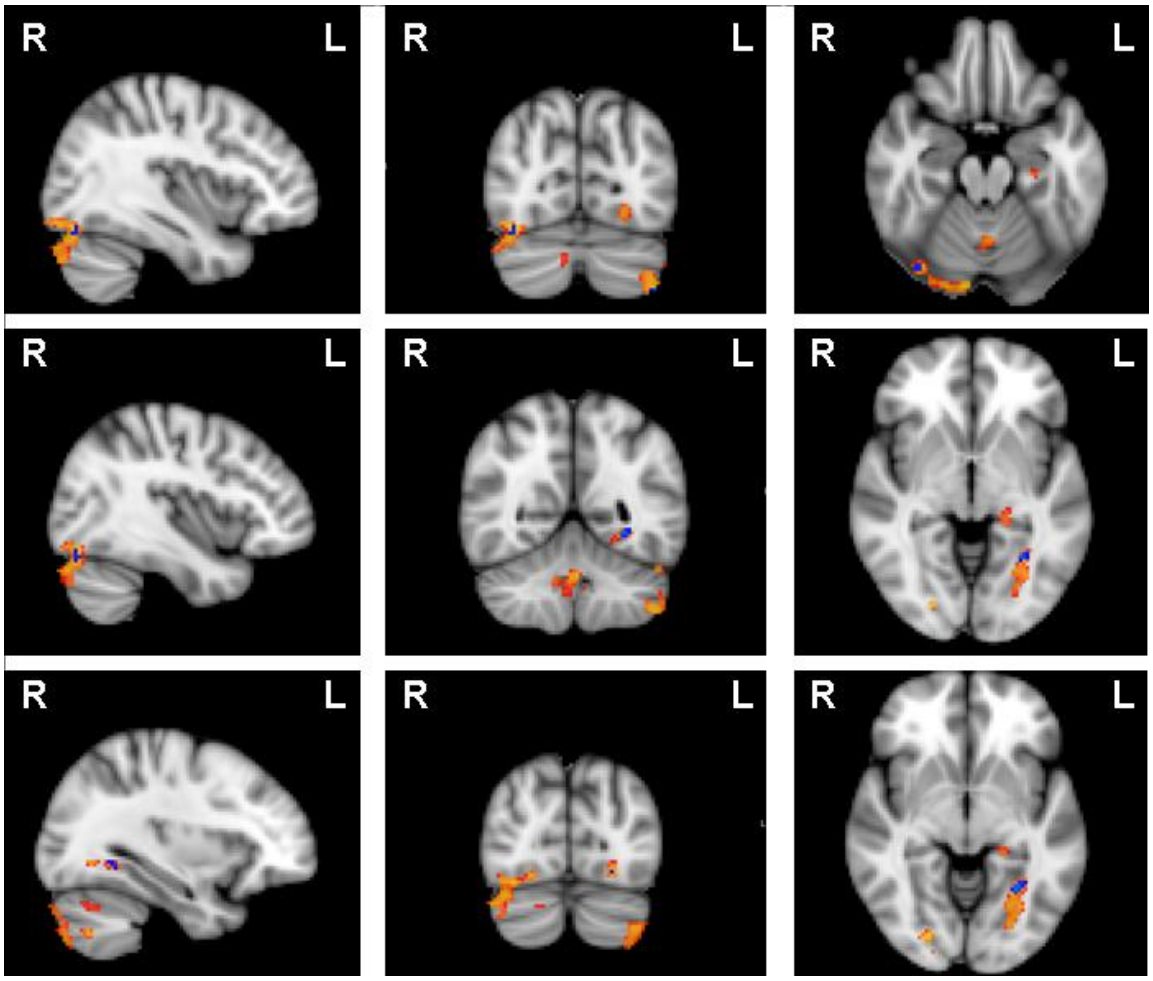
	Median Split of Fitness Variable							
	Low Fitness (N=15)				High Fitness (N=14)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Age	67.20	5.56	60	81	69.64	6.37	60	85
Education	15.67	2.77	12	20	16.64	1.78	14	20
Gender		12 female				6 female		
PA	156.19	142.39	0	460	335.71	224.80	120	900
Fitness	0.42	0.17	0.19	0.66	0.68	0.16	0.42	1.01
MMSE	28.87	1.13	27	30	29.07	0.83	27	30
Executive	0.08	0.66	-1.05	1.14	-0.09	0.74	-1.19	1.02

Notes: SD = standard deviation; PA = physical activity variable; MMSE = Mini Mental State Examination; Executive = Blom-transformed executive function composite



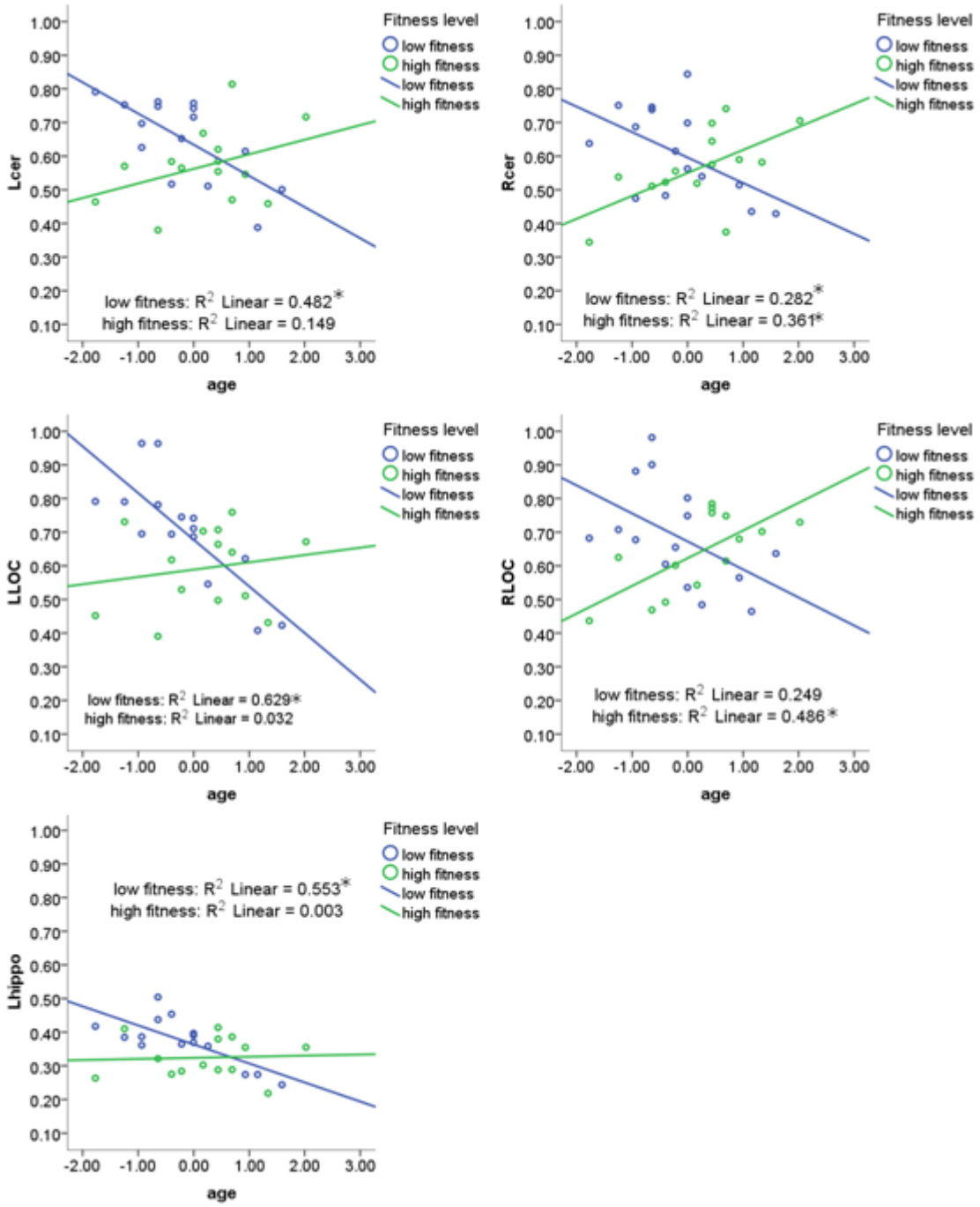
3-1 Age X fitness interaction: Significant clusters

Red/orange regions depict the areas in which fitness$_{\text{-age}}$ moderated the relationship between age and gray matter volume. These regions correspond to the right (Rcer) and left cerebellum (Lcer), left hippocampus/parahippocampal gyrus (Lhippo), and right inferior lateral occipital cortex/occipital fusiform gyrus (RLOC) and left inferior lateral occipital cortex/occipital fusiform gyrus/lingual gyrus (LLOC).



3-2 Age X fitness interaction: Overlap between two regression models

The areas in blue represent clusters in which the interaction between age and fitness$_{\text{-age}}$ was significant (TFCE p<.05) from a multiple regression model in which fitness$_{\text{-age}}$, physical activity, age X fitness$_{\text{-age}}$ and age X physical activity predicted voxel-wise gray matter volume. The regions in orange represent the significant interaction between age and fitness$_{\text{-age}}$ derived from the multiple regression model in which fitness$_{\text{-age}}$, age, executive function, and age X fitness$_{\text{-age}}$ predicted voxel-wise gray matter volume. It can be seen that the areas in blue are much smaller than those in orange, but are encompassed by the same anatomical regions as the significant areas from the previous analysis. Thus the interaction between age and fitness$_{\text{-age}}$ was a better predictor of gray matter volume than self-reported physical activity and its associated interaction with age.



3-3 Age X fitness interaction: Scatter plots

Y-axis depicts mean gray matter volume extracted from each of the five ROIs resulting from the age X fitness$_{\text{-age}}$ interaction (Figure 3-1). X-axis represents Blom transformed age, where -2 = 60; -1 = 61; 0 = 68; 1 = 74; and 2 = 85. High and low fitness lines are based on a median split for the fitness$_{\text{-age}}$ variable. Lcer = left cerebellum; Rcer = right cerebellum; LLOC = left inferior lateral occipital cortex/occipital fusiform gyrus/lingual gyrus; RLOC = right inferior lateral occipital cortex/occipital fusiform gyrus; Lhippo = left hippocampus/parahippocampal gyrus. * Indicates the linear trend is significant at the p<.05 level.

CHAPTER 4
LIFE-PILOT STUDY DATA

Methods

The LIFE-P Study

The Lifestyle Interventions and Independence for Elders – Pilot study (LIFE-P) was a single-blinded randomized control trial of physical activity that lasted 1 year and was conducted at four different institutions: Cooper Institute, Stanford University, University of Pittsburgh, and Wake Forest University (Pahor et al., 2006). The intervention consisted of random assignment of sedentary older adults into two groups: a moderate-intensity physical activity intervention (PA) or a health education successful aging (SA) group. The original trial collected data from 424 participants.

Physical activity intervention (PA)

The PA intervention consisted of a combination of aerobic, strength, balance, and flexibility exercises and it was divided into three phases: adoption (weeks 1-8), transition (weeks 9-24), and maintenance (weeks 25 to end of trial). During the adoption phase, three center-based exercise sessions (40-60 minutes) per week were conducted within a supervised setting. The transition phase consisted of 4 months in which the number of center-based sessions was reduced to 2 times/wk and home-based endurance/strengthening/flexibility exercises (≥3/wk) commenced. During the maintenance phase, the intervention was home-based, with optional once-to-twice-per-week center-based sessions and monthly telephone contact. Walking was the primary mode of exercise with a goal of at least 150 minutes per week in which moderate intensity exercise was encouraged (13 on the Borg scale).

Successful aging intervention (SA)

The SA intervention served as the active control group for the PA group and was designed to provide attention and health education. Participants met in small groups weekly for the first 26 weeks and then monthly. Topics of discussion included nutrition, medications, foot care, and recommended preventative services at different ages. Basic educational information related to physical activity was provided. Each session ended with a short 5-10 minute intervention of gentle upper extremity exercise.

LIFE-P inclusion criteria

Participants between the ages of 70-89 years who had a sedentary lifestyle at baseline (<20 minutes/wk of structured PA during the past month) were included in the LIFE-P study. All participants had to be able to walk 400 m within 15 minutes without sitting or using an assistive device. A score of 9 (on a scale of 0-12) was needed in the Short Physical Performance Battery, as well as having completed behavioral tests that logged health behavior for one week. All participants gave informed consent, lived in the study area, and were not planning to move for at least 9 months.

The LIFE-P Follow-up Brain Imaging Study

This follow-up study was conducted using a subsample of the LIFE-P subjects from the Pittsburgh site. The details of the study can be found elsewhere (Rosano et al., 2010), but the main aspects pertinent to the current study are presented here. At the Pittsburgh location, 104 participants completed the LIFE-P trial. Two years after termination of the LIFE-P study, participants were screened for interest in participation in a follow-up functional magnetic resonance imaging (fMRI) study. Only participants who reported to have remained adherent to their original group assignment (PA or SA) after the LIFE-P study were eligible for the follow-up fMRI study. To measure adherence

to original group assignment, participants originally assigned to the PA group were asked: “Since the LIFE-P study ended, have you completely stopped your regular physical activity?” and participants were included if they responded “No.” The SA group was asked the question: “Since the LIFE-P study ended, have you spent at least 20 minutes a week getting regular exercise? Regular exercise includes activities like: brisk walking, jogging, weight lifting, cycling, aerobics, or dancing” and they were included if they responded “No.” To corroborate the participant’s responses regarding adherence to their original group assignment, current physical activity levels were measured via the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire (Stewart, Verboncoeur, & McLellan, 2001). The CHAMPS measures the participation (yes or no) and frequency (days/wk and hours/day) for the following activities: walking leisurely, walk for errands, ride a bicycle, use aerobic machines, exercise (strength and water exercise), stretching, and general conditioning. Mean kilocalorie expenditures were computed using the CHAMPS. Kilocalorie expenditures were computed from the following activities: walk leisurely, walk for errands, ride a bicycle, use aerobic machines, do water exercise, stretching, heavy strength exercise, light strength exercise, and general conditioning.

The main purpose of the follow-up study was to compare the functional brain activity level of the PA and SA groups during an executive function task (Digit Symbol Substitution Test: DSST) two years after the LIFE-P intervention ended, to assess the long-term effects of adherence. It was found that participants in the PA engaged in more minutes of physical activity and had higher DSST scores than the SA group two years following the intervention. The PA group also displayed more brain activity in areas

associated with processing speed, such as the left dorsolateral prefrontal cortex, posterior parietal, and anterior cingulate cortex (Rosano et al., 2010).

Thirty participants who remained adherent to their original LIFE-P assigned group were included in this follow-up fMRI study (20 from the PA and 10 from the SA group). These participants underwent fMRI and a clinical exam. Age did not differ significantly between the PA and SA groups (80.8 & 81.45 respectively, p=.5) in the follow-up subsample, although DSST accuracy and response time during the fMRI was significantly different between the groups (see Rosano, et al. 2010 for details).

The Current Brain Imaging Study

The current study used a subsample of the LIFE-P follow-up fMRI study to compare the gray matter volume and cognitive performance between the PA and SA groups in an attempt to supplement our cross-sectional findings. We hypothesized that the PA group would show higher levels of gray matter volume in frontal, temporal, and parietal areas when compared to the SA group, given the protective effect of exercise on brain health (Colcombe et al., 2006).

Participants

The current study included data from 20 participants out of the 30 available from the LIFE-P follow-up fMRI study. Data were from 10 participants from the PA and 10 from the SA groups. Given that VBM analyses necessitate the creation of study-specific templates, the sample size of each group must be equal in order for the study-specific template to accurately represent each group. From the 20 structural images available in the PA group, 10 were selected by matching to the SA group by age. The resulting groups did not differ significantly in age, calories expended in all exercise-related activities, or score in the DSST, although the mean amount of calories expended in all

exercise-related activities and performance in the DSST was higher in the PA than SA group. See Table 4-1 for participant characteristics.

Data Analyses

Behavioral Analysis

Independent samples T-tests were carried out on PASW to compare the PA and SA groups on age, calories expended in all exercise-related activities, and accuracy/reaction time on the DSST.

Structural Images

All MRI images were collected as described in Rosano, et al., 2010. A 3-Tesla Siemens Trio MR scanner with a 12-channel head coil was used. For the purposes of the current study, only T1-weighted images were used in order to perform the VBM analysis. T1-weighted images were three-dimensional magnetization prepared rapid gradient echo (TR=2.3 seconds; TE=3.43 ms; slice thickness=1mm; 176 slices). All structural images were pre-processed following the same procedures outlined on Chapter 3, data analyses section: structural images - image preprocessing. The only difference is that the current study-specific template was comprised of the 20 participants derived from this sample rather than the participants in the cross-sectional sample. The resulting registered and modulated gray matter images were smoothed at 4.6 mm FWHM.

The GLM higher level/non-time series analysis option in FSL was used to carry out voxel-wise group comparisons between the PA and SA groups using randomize, which corrects for multiple comparisons using a threshold-free cluster enhancement method (TFCE) via permutation analyses. The following comparisons were modeled: PA-SA & SA-PA. Given our small sample size we also calculated voxel-wise Cohen's *d* values to

report effect sizes using the following formula on fslmaths: *d*=2t/df, where df is the degrees of freedom for the Ttest or 2n-2; where n=# of participants in each group (df=18).

Results

Group Comparisons: Demographics and Performance

Mean age did not differ between the PA (*M*=81.11, *SD*=3.05) and SA (*M*=81.56, *SD*=2.77) groups, *t*(18)=-.342, *p*>.05, Cohen's *d*=-.04. Calories expended in all exercise-related activities at the time of follow-up did not differ significantly between the PA (*M*=2504.79, *SD*=1426.11) and SA (*M*=1587.23, *SD*=905.83) groups, *t*(18)=1.72, *p*>.05, Cohen's *d*=.19. Similarly, there was no significant difference between the PA (*M*=81%, *SD*=15%) and SA (*M*=66%, *SD*=27%) groups on accuracy during the DSST, *t*(18)=1.47, *p*>.05, Cohen's *d*=.21. Reaction time during the DSST did not differ between the groups (PA: *M*=1836.79 ms, *SD*=356.84 ms; SA: *M*=2167.14, *SD*=507.12), *t*(18)=-1.68, *p*>.05, Cohen's *d*=-.19.

Group Comparisons: Gray Matter Volume

There were no gray matter regions that differed significantly between the groups after correcting for multiple comparisons (TFCE *p*<.05). See Appendix (Figure 6-2) for median effect sizes per ROI.

Discussion

We used data from an independent exercise intervention study in an attempt to verify our cross-sectional findings and assess the relationship between physical activity level and brain density between groups previously assigned to a moderate-intensity physical activity intervention (PA) versus a health education successful aging group (SA). We hypothesized that participants previously assigned to the PA intervention

group would display greater gray matter volume than those assigned to the SA group, especially in areas vulnerable to brain aging (e.g., frontal, temporal, parietal lobes). Results indicated that there were no significant differences between the two groups on gray matter volume, nor did they differ significantly on their performance on an executive function measure (DSST) or calories expended in all exercise-related activities.

The fact that we did not find significant differences between the exercise and control groups is probably due to the small sample size included in this study, which affects the power needed to detect significant differences. Similarly, the lack of differences may have been due to the fact that physical activity level was measured via self-reported adherence to a physical activity intervention that took place two years prior to the follow-up fMRI study. It is possible that participants either over or underestimated their current level of physical activity and their adherence to the previous intervention. If this is the case, then the PA and SA groups may not be that different from each other and we should not expect to find significant differences in gray matter volume. Moreover, incorporating a measure of fitness level rather than self-reported physical activity would have helped to corroborate participants' self-report.

Future intervention studies should measure the moderating effect of increased fitness level on the relationship between gray matter volume and age. Similarly, measures of cardiovascular fitness, as well as objective assessments of physical activity (e.g. actigraphy), should be carried out in future intervention studies, given the limitations of self-reported measures. Moreover, exercise interventions should include a long-term follow up period in which the same measures obtained at baseline and study

termination are collected. In this way, a physical activity monitoring period can be assessed at follow-up in an objective fashion (actigraph).

4-1 LIFE-P participant characteristics

	Physical Activity (N=10)		Successful Aging (N=10)							
	M	SD	M	SD	*t*	df	*p*	M diff	SE	*d*
Age	81.11	3.05	81.56	2.77	-0.34	18.00	0.74	-0.45	1.30	-0.04
Edu	14.00	2.83	14.40	2.07	-3.61	18.00	0.72	-0.40	1.11	-0.40
Gender	8 female		7 female		0.27*	1.00	0.61			
Kcal	2504.79	1426.11	1587.23	905.83	1.72	18.00	0.10	917.56	534.26	0.19
DS-A	0.81	0.15	0.66	0.27	1.47	*14.18*	0.16	0.15	0.10	0.21
DS-RT	1836.79	356.84	2167.14	507.12	-1.68	18.00	0.11	-330.36	196.09	-0.19

Notes: M = mean; SD = standard deviation; df = degrees of freedom; M diff = mean difference; SE = standard error of the difference; *d* = Cohen's *d*; Edu = education; Kcal = total amount of calories expended in all exercise-related activities (CHAMPS); DS-A = digit symbol substitution test-accuracy; DS-RT = digit symbol substitution test-reaction time. * = Pearson Chi-Square value; *df: equal variances not assumed*.

CHAPTER 5
GENERAL DISCUSSION

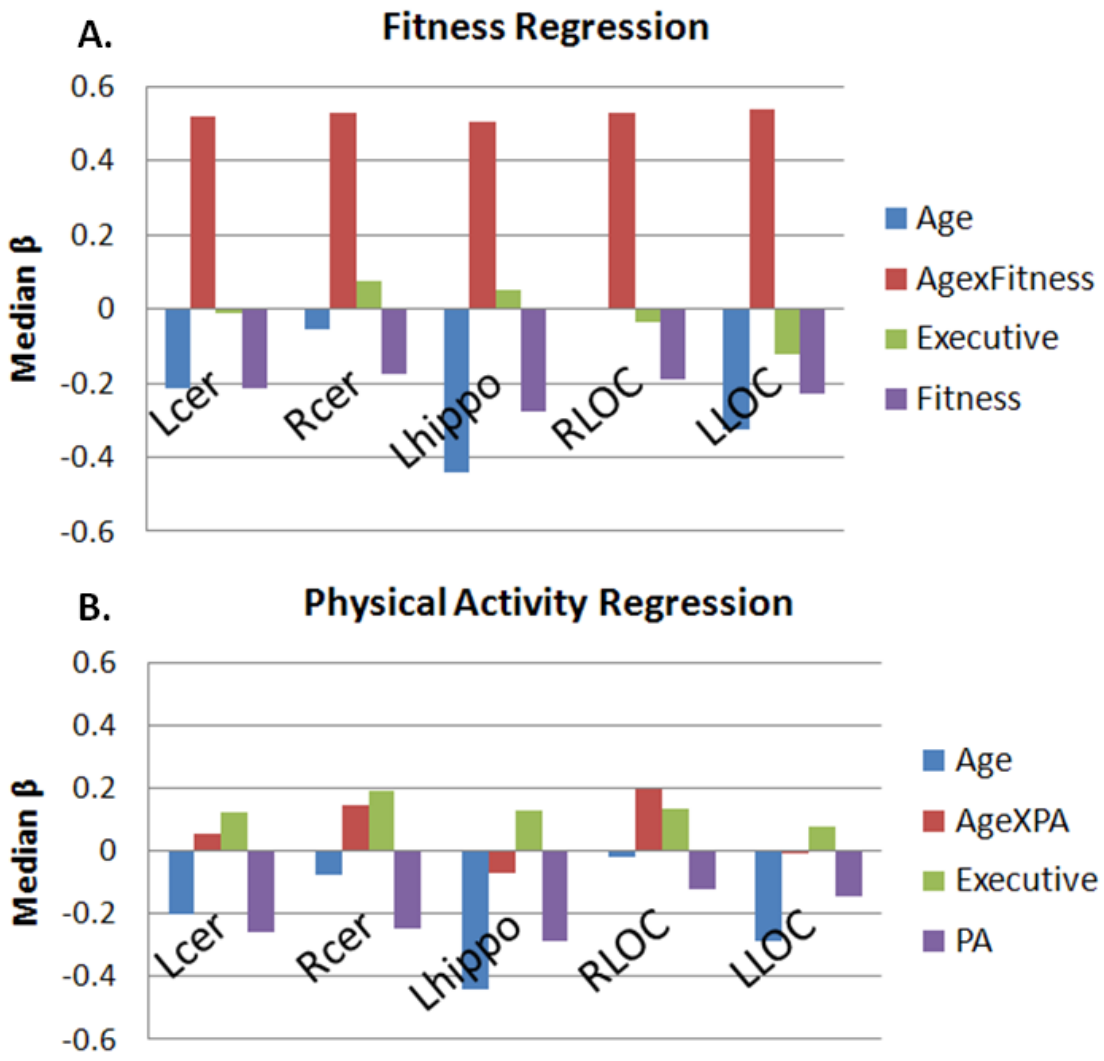
Age-related cognitive decline occurs as the aging brain experiences decrements in gray and white matter volumes, which affect networks needed to perform higher order cognitive functions. It has been shown in the literature that exercise and increased levels of physical activity can mitigate brain aging and thus help protect against cognitive decline in late-life. The current study investigated the differential effect of self-reported physical activity and fitness level on gray matter volume using VBM, while concurrently measuring the direct association between gray matter volume and executive function in a cross-sectional sample of older adults. In an attempt to verify our findings, we analyzed structural brain data from a sub-sample of an independent exercise intervention study (LIFE-P) which also collected performance on a measure of executive function in older adults previously assigned to a physical activity (PA) or a successful aging health education intervention (SA).

Findings from the cross-sectional study suggest that fitness level moderated the relationship between age and gray matter volume. Fitness level displayed a protective role on gray matter volume as a function of age bilaterally in the cerebellum and fusiform/inferior lateral occipital cortex/lingual gyrus, and left hippocampus and parahippocampal gyrus. These regions have been shown to decline as a function of age, and we were able to find that fitness level mitigated this effect in our cross-sectional sample. Executive function did not predict the amount of gray matter volume in any area of the brain, nor did gray matter volume predict executive function performance above and beyond the contribution of age. Lack of power within the LIFE-P follow-up study prevented us from finding significant differences between the PA and

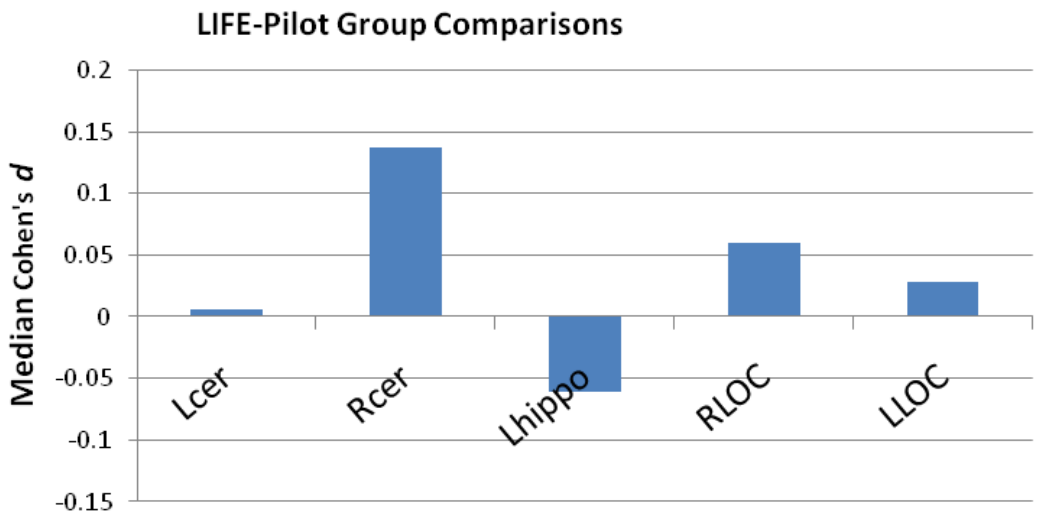
SA groups at the whole-brain level and behaviorally. This problem was possibly exacerbated by the fact that the measure used to assign participants to groups was based on self-reported physical activity and adherence to an intervention that took place two years prior to the current study.

In sum, the current study shows that, consistent with the literature, fitness level provided a protective role against brain aging by sparing gray matter tissue loss in those with higher fitness level in a cross-sectional sample. The same was not true for data obtained from an exercise intervention study; however the lack of findings is most likely due to our small sample size and the self-report nature of the measure used to select the groups. Future exercise and aging studies should be interventional in nature to capture intra and inter-individual change in brain structure, function, and cognitive performance. Moreover, future investigations should study the changes that occur in the relationship between gray and white matter volumes as fitness level increases. This would help us to better understand the dynamic changes that occur as the aging brain becomes more plastic following exercise. Furthermore, fitness ($VO2_{max}$), objective physical activity (i.e., actigraphy), and cognition should be properly assessed and standardized in the literature to facilitate comparisons between studies and thus reduce methodological variability. Future exercise intervention studies should rely on objective measures of fitness level (i.e., $VO2_{max}$ or estimates thereof) rather than on self-reported measures of physical activity.

APPENDIX



6-1 Median effect sizes per region of interest (cross-sectional study)



6-2 Median effect sizes per region of interest (LIFE-P)

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BIOGRAPHICAL SKETCH

Zvinka Zoe Zlatar received her Bachelor of Arts degree in psychology from the University of Nevada, Las Vegas in 2005 and her Master of Science degree in psychology from the University of Florida in the spring of 2009. Zvinka is currently a fourth-year neuropsychology graduate student in the University of Florida's Clinical and Health Psychology program. She works in the Brain Imaging Rehabilitation and Cognition lab under the supervision of Bruce Crosson, Ph.D. and has been funded by the National Institute on Aging through both a supplemental grant awarded through the Claude D. Pepper Older Americans Independence Center, and the University of Florida’s Aging Training T-32 fellowship. Zvinka’s research focuses primarily on studying neurocognitive aging in healthy older adults using both functional and structural magnetic resonance imaging (MRI). Zvinka is also interested in investigating life-style factors that can potentially mitigate age-related cognitive decline, such as exercise and changes in physical activity levels.