THE RELATIONS BETWEEN PHYSICAL ACTIVITY, EXECUTIVE FUNCTION, AND WHITE MATTER INTEGRITY IN OLDER ADULTS

by

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(Under the Direction of L. Stephen Miller)

ABSTRACT

The world's population of older adults is steadily increasing as people begin to live longer (Murman, 2015). There is a need to examine lifestyle changes that may prevent or slow down age-related cognitive decline. Physical activity is associated with better cognitive function in older adults (Colcombe & Kramer, 2003), particularly better executive function (Angeveran et al., 2008; Smith et al., 2010; Sherder et al., 2014). There is reason to believe that white matter integrity may mediate these changes (Grieve et al., 2007; Daselaar et al., 2015). In the current study, level of physical activity and steps in healthy older adults was measured. Diffusion tensor imaging (DTI) was utilized to examine white matter integrity, and neuropsychological testing was used to examine level of executive functioning. Results indicated that average steps were significantly related to executive function (t=2.829, p=.007), while moderate to vigorous physical activity (MVPA) was not (t=1.772, p=.08). White matter integrity, measured globally and in regions-of-interest (ROIs) did not mediate the associations between MVPA or average steps and executive function. These results suggest that white matter integrity alone may not be the mechanism by which physical activity impacts executive function in healthy older adults, and future research should examine additional health risk factors that may contribute.

INDEX WORDS: aging, white matter integrity, physical activity, executive function

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BS, Emory University, 2015

BA, Emory University, 2015

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2019

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May 2019

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CHAPTER 1

INTRODUCTION

The proportion of older adults in the population is expected to steadily increase as people continue to live longer (Ortman, Velkof, & Hogan, 2014). With this increase, it is imperative to continue to understand and prevent cognitive decline associated with aging. Most older adults are likely to experience some loss of brain volume and cognitive functioning due to normal aging (Good et al., 2001; Salthouse, 2003); therefore, there is a need for interventions to slow down cognitive decline and preserve brain integrity in older adults. There is evidence that physical activity may serve as a protective factor against cognitive and physical decline and may even be protective against chronic diseases such as diabetes and cardiovascular disease that have become relatively common in adults as they age (Kujala, 2011). There is reason to believe that physical activity may be a relatively simple and cost-effective lifestyle change that could provide cognitive benefits in later life. Multiple meta-analyses have found that aerobic exercise training has robust but selective effects on cognitive function in healthy older adults (Colcombe & Kramer, 2003; Smith et al., 2010; Angeveran et al., 2008). In particular, more physical activity in older adulthood has been shown to be positively correlated with episodic memory performance (Hayes et al., 2015a; Smith et al., 2010), spatial working memory (Oberlin et al., 2015, Wong et al., 2015; Erikson et al., 2011), verbal memory (Nagamatsu et al., 2013), and executive function (Liu-Ambrose et al., 2010). Increasing physical activity in older adults holds promise for slowing down the cognitive decline associated with aging.

Cognition and Aging

The normal aging process typically involves modest decline over time in certain cognitive abilities such as conceptual reasoning, processing speed, and acquiring and retrieving memories, while other cognitive abilities such as crystallized intelligence remain relatively stable (Salthouse, 2010; Harada, Natelson Love, & Triebel, 2014). This pattern of decline is consistent with the retrogenesis hypothesis of aging, which posits that areas of the brain where white matter fibers myelinated first in brain development are more robust than areas of the brain where fibers myelinated later; thus, these areas of early myelination are less susceptible to damage over time (Stricker et al., 2009; Brickman et al., 2012). This theory provides evidence for why there is a decline in cognitive abilities associated with frontal areas first in aging (e.g., working memory, reasoning), as these areas are some of the last to myelinate over the course of brain development (Arain et al., 2013). Frontal areas are implicated in higher order processing, typically referred to as executive function (Otero & Barker, 2014). Executive function is an extremely important neuropsychological domain, especially given its positive associations to functional ability in later life (Razani et al., 2007). While some amount of age-related frontal decline is thought to be typical, there is evidence that certain activities may prevent or reduce age-associated cognitive decline over time. The theory of cognitive reserve hypothesizes that by using pre-existing cognitive processing approaches or by employing compensatory approaches, the brain can tolerate age related changes while still maintaining function (Stern, 2002; Stern, 2012). There are several aspects that are thought to contribute to increased cognitive reserve including higher education level, higher occupational level, increased participation in activities (e.g., physical, social, and mental), and higher socioeconomic status (Stern, 2012). Another theory, the Scaffolding Theory of Aging and Cognition (STAC), posits that healthy older adults are affected by varying degrees of neural degradation as they age, and the level of cognitive function a healthy older adults display is a combination of degradation and beneficial processes termed compensatory scaffolding (i.e., neurogenesis, distributed processing, recruitment of brain regions). This compensatory scaffolding is thought to be enhanced by lifestyle factors such as physical activity and new learning (Reuter-Lorenz & Park, 2014). The current knowledge of the relations between cognition and aging continues to expand and is supplemented by research examining the relations between aging and brain changes.

Aging and Brain Integrity

There are several different methods that exist to examine the integrity of the aging brain. One of these methods includes diffusion tensor imaging (DTI). DTI measures the movement of water in brain tissue to estimate the connective integrity of white matter tracts. The degradation of white matter integrity in aging disrupts neural transmission and has been related to negative cognitive outcomes (Brickman et al., 2006). Research suggests that DTI may detect changes in white matter integrity before volumetric changes can be detected (Hugenschmidt et al., 2008; Canu et al., 2010). Additionally, microstructural changes have been detected in white matter tissue in healthy older adults as well as older adults with mild cognitive impairment who have no obvious degradation measurable via other imaging means (Bosch et al., 2012; Canu et al., 2011; Burzynska et al., 2010; Gold et al., 2010). Therefore, DTI is a fairly sensitive method for examining the integrity of the aging brain.

DTI involves the acquisition of diffusion-weighted images across time. The quantification of DTI utilizes a three-dimensional ellipsoid with a primary axis (λ_1) and two additional axes (λ_2 and λ_3) depicting the magnitude and orientation of the diffusion of water. Water moves primarily in an anisotropic fashion, or along one direction, in white matter areas of the brain (see Figure 1). This is because the movement of the water is physically constrained by the myelin sheath, which constrains the movement of water to be primarily parallel rather than perpendicular to the tract (Chanraud et al., 2010). Therefore, the quantification of the movement of water in the brain can provide valuable information about the structural integrity of white matter fiber tracts (Soares et al., 2013). DTI research primarily uses four metrics to describe anisotropy: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). These metrics will be discussed in detail.

FA specifically measures the diffusivity of water along the primary axis (λ_1) relative to the other two axes (λ_2 and λ_3) of the chosen ellipsoid; thus, higher FA values represent greater anisotropy and coherence (Chaunraud et al., 2010). A common metric used in DTI research, FA has been shown to be sensitive to microstructural changes in the aging brain, particularly in anterior regions (Madden, Bennet, & Song, 2009; Alexander et al., 2008; Bennett et al., 2010). Healthy older adults show declines in FA in regions such as the corpus callosum, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and cingulate bundle, which are all tracts that have connections with the frontal lobes (Teipel et al., 2010). Alterations in FA involve many factors such as demyelination, decreased axon density, and axonal membrane integrity (Beualieu, 2002). Like FA, MD is another commonly used DTI metric. MD is the average amount of water diffusion across all three axes. Therefore, higher levels of MD represent greater isotropy and perhaps decreased white matter integrity. Several studies have shown that there are age-related increases in MD, that, like FA, occur first in anterior regions of the brain (Head et al., 2004; Salat et al., 2005; Yoon et al., 2008).

Other utilized DTI metrics are RD and AD. RD represents an average of the diffusion along the two secondary axes (λ_2 and λ_3). This metric is thought to capture the movement of water perpendicular to the white matter tract (Chaunraud et al., 2010) and may be an indication of the degree of myelination (Budde et al., 2005; Song et al., 2002). Previous research utilizing DTI in aging adults has shown that age-related decreases in FA are associated with increases in

RD in frontal regions (Davis et al., 2009). AD, on the other hand, has mixed findings in past aging research. AD represents the amount of diffusion along the primary axis and is thought to reflect axonal integrity (Budde et al., 2007; Beaulieu, 2002). While some studies have found that AD increases with normal aging (Bennett et al., 2010), others have found that AD does not increase with normal aging (Davis et al., 2009; Bhagat & Beaulieu, 2004), or may actually decrease (Burzynska et al., 2009; Bennett et al., 2010). Currently, the nature of the association between AD and changes in normal aging is not well understood, although some evidence indicates that patterns of associations likely vary by brain region and may reflect the macrostructural properties of white matter (Bennett et al., 2010).

Brain Integrity and Cognitive Function in Older Adults

Preserved brain integrity in older adults has been shown to be related to better cognitive function in a variety of domains including executive function (Grieve et al., 2007; Daselaar et al., 2015), spatial memory (Erikson et al., 2011; Oberlin et al., 2015), processing speed (Madden, Bennet, & Song, 2009; Vernooij et al. 2009), and episodic memory (Daselaar et al., 2015). FA measured in the centrum semiovale, a white matter tract superior to the corpus callosum, has been shown to be positively correlated with overall cognitive ability in older adults (Shenkin et al., 2003). Additionally, better spatial working memory in older adults has also been shown to be related to higher FA in tracts that facilitate intrahemispheric communication between the medial temporal lobe and the prefrontal cortex (Oberlin et al., 2015). Low episodic memory performance in older adults has been shown to be associated with reduced FA in white matter tracts in the medial temporal lobe (Daselaar et al., 2015). Finally, lower FA has been shown to be related to worse processing speed and motor speed (Vernooij et al., 2009). These studies illustrate that there are several domains of cognitive function that have an association with brain integrity as measured by white matter indices.

There is a plethora of research indicating that brain integrity is especially important in the preservation of executive function in older adults. An important study by Grieve and colleagues (2007) explored the relations between FA and various cognitive measures that were tested across a wide range of ages of participants. They found associations between decreased FA in prefrontal cortex white matter tracts, increased age, and worse executive function. In addition, RD in frontal, temporal, parietal, and occipital white matter tracts has also been found to be associated with executive functioning, processing speed, and visual scanning in older adults (Jacobs et al., 2013). Similarly, Daselaar and colleagues (2015) found reduced FA in prefrontal cortex white matter tracts associated with lower executive function in older adults. These findings indicate associations between white matter integrity and executive function in older adults. Additionally, there is evidence that this relation may be one of the first detectable changes in normal age-related cognitive decline, due to the primary decline in white matter integrity in anterior brain regions (Stricker et al., 2009; Brickman et al., 2012), indicating a good target for intervention.

Physical Activity and Executive Function in Older Adults

There is evidence of a specific relation between increased physical activity and better executive function in healthy older adults. Much of this research has been done by utilizing exercise interventions targeted for older adults. A meta-analysis by Colcombe and Kramer (2003) found that the largest gains in cognitive function following aerobic fitness training in older adults were specific to executive control. More recent meta-analyses have also found that exercise interventions in older adults benefit primarily executive function (Angeveran et al., 2008; Smith et al., 2010; Sherder et al., 2014). Additionally, Nishiguchi and colleagues (2015) found that healthy older adults who participated in a twelve-week exercise program had significantly greater post-intervention improvements in executive function than the sedentary control group. While exercise interventions have been shown to improve executive functioning in healthy older adults, there is also evidence that initiating an exercise program in older adults with mild cognitive impairment can improve executive function, perhaps indicating that physical activity may have preventative as well as therapeutic effects (Lawla et al., 2014; Baker et al., 2010; van Uffelen et al., 2008). Other research has examined self-reported or measured current level of physical activity and its association to cognitive function. Interestingly, a recent study found that the intensity of physical activity that older adults engaged in over a span of one week rather than quantity had an impact on executive function, such that older adults that engaged in more intense physical activity performed better on an executive function measure than those that did not (Brown et al., 2012). There is also evidence that older adults who are simply more mobile during the day have better executive functioning than older adults who are more sedentary (Barnes et al., 2008). Importantly, physical activity level as measured by one week of wearing an accelerometer was related to performance on the Trail Making Test (TMT), a measure of executive function (Kerr et al., 2013). Because there is extensive evidence for exercise interventions improving executive function in older adults and several studies have shown associations between increased physical activity in older adults and better executive function, there is reason to explore this association in the context of underlying brain mechanisms that may mediate this relation.

Physical Activity and Brain Integrity in Older Adults

Not only have exercise interventions been shown to improve cognitive function in older adults, but they have also been shown to improve neural efficiency and white matter integrity. Nishiguchi and colleagues (2015) found that less activation occurred in the prefrontal cortex and areas associated with short-term visual memory during an fMRI visual memory task after older adults had participated in a twelve-week exercise intervention, indicating increased neural efficiency following the implementation of an exercise intervention for older adults. This decreased activation corresponded with improvements in memory and executive function, indicating that exercise interventions may have a positive impact on neural efficiency. Further, a study by Voss and colleagues (2013) found that a one-year exercise intervention for older adults resulted in improvements in white matter integrity in the frontal and temporal regions that occurred irrespective of changes in cognitive function. Recently, other forms of exercise interventions, such as dance, have been shown to improve brain integrity in older adults, particularly in the fornix (Burzynska et al., 2017). Additionally, several studies have examined the relation between physical activity and white matter integrity in older adults using self-reported or measured current level of physical activity. A recent study found that self-reported physically active older adults who were not carriers of the APOE-ε4 gene had greater FA and lower RD than older adults who reported less physical activity, indicating that physical activity may preserve white matter integrity in healthy older adults not at increased risk for Alzheimer's disease (Smith et al., 2015). Additionally, Hayes and colleagues (2015b) found that cardiorespiratory fitness in healthy older adults was positively associated with white matter integrity in multiple brain regions including white matter tracts in frontal and temporal lobes. There is also some evidence that physical activity over a relatively short period of time may be neuroprotective. A recent study found that white matter integrity decline in older adults over a six-month period was lesser in magnitude for older adults who were less sedentary and engaged in moderate to vigorous physical activity (Burznyska et al., 2017). Of importance to the current study, a recent study that showed a positive association between light physical activity, as measured by an accelerometer, and white matter integrity in temporal regions (Burzynska et al., 2014).

Physical Activity Mechanisms of Change

There are many theories about what mechanisms are responsible for the changes in brain integrity and cognitive function brought about by physical activity and exercise interventions in older adults. Some research provides evidence that physical activity and exercise interventions directly changes the structure of the brain, and thus improves cognitive function through this avenue. Colcombe and colleagues (2006) found that a six-month exercise intervention for older adults resulted in significant increases in white and grey matter volume in various brain regions that did not also occur in the non-exercising control group. Similarly, Erikson and colleagues (2011) found that an exercise intervention for older adults led to increased hippocampal volume which was related to improvements in spatial memory. Additionally, white matter integrity has been shown to mediate the relations between cardiorespiratory fitness and spatial working memory in older adults (Oberlin et al., 2015). Finally, increased neural efficiency associated with an exercise intervention for older adults has been shown to mediate the positive relations between physical activity and performance on visual memory and dual-processing tasks (Nishiguchi et al., 2015; Wong et al., 2015). These studies illustrate the idea that physical activity and exercise interventions in older adults may be directly changing the structure and efficiency of the brain, thereby impacting cognitive outcomes.

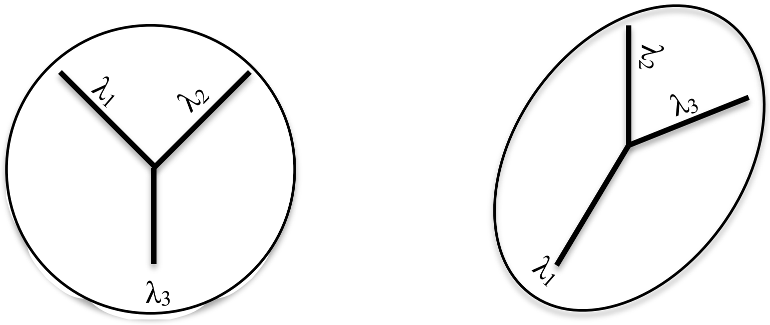
Other studies have examined neuroprotective factors that are upregulated and changes in blood flow in the brain that are associated with increased physical activity and exercise interventions. Several studies, especially using animal models, have found that exercise leads to increased brain derived neurotrophic factor (BDNF), which has been shown to be protective for neuronal tissue (Erikson et al., 2011; Otsuka et al., 2016; Lawson et al., 2014; Intlekofer & Cotman, 2013). Therefore, increased physical activity and exercise interventions in older adults may be contributing to increased BDNF, and thus preservation of brain tissue. Additionally, greater physical activity in older adults has also been correlated to improved cerebral perfusion (Rogers, Meyer, & Mortel, 1990). Inadequate cerebral perfusion has negative consequences for cognitive functioning in older adults (Efimova et al., 2008), and thus, physical activity and exercise interventions may preserve cognitive function through improved blood flow in the brain. There are many possible mechanisms of change brought about by physical activity and exercise interventions including structural brain changes, neuroprotection, and cerebral perfusion that may be responsible for the changes in cognitive function. These mechanisms should be kept in mind when examining the relations between physical activity and executive function, as there is evidence that physical activity and exercise interventions may be preserving cognitive function by preserving brain integrity.

Current Study

Given the potential for physical activity to preserve brain integrity and cognitive function, there is a need to examine whether physical activity in later life as measured by an accelerometer is related to greater executive function through preserved white matter integrity. Based on previous literature, we predicted that higher levels of physical activity would be associated with better executive function ability in a group of healthy older adults. We also predicted that the association between increased physical activity level and better executive function would be mediated by preserved white matter integrity (Figure 2), particularly in regions-of-interest (ROI) that include tracts that have been implicated in aging (i.e., corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, cingulum, fornix) (Teipel et al., 2010). White matter integrity was defined as higher FA, lower MD, and lower RD (Chaunraud et al., 2010). While AD was measured, no directional hypothesis was made due to the mixed findings on the relations between AD and aging.

Table 1. Descriptive Statistics

Variable	% or M (SD)
Demographics	
Age	73.05 (5.68)
Sex (% female)	67.4%
Race (% White)	95.3%
Years of Education	17.21 (2.32)
Average MVPA (seconds/day)	778.55 (993.77)
Average Steps (day)	5500.56 (3210.42)
DKEFS Composite	11.78 (2.24)



Isotropic

Anisotropic

Figure 1. Isotropic and anisotropic movement in Diffusion Tensor Imaging

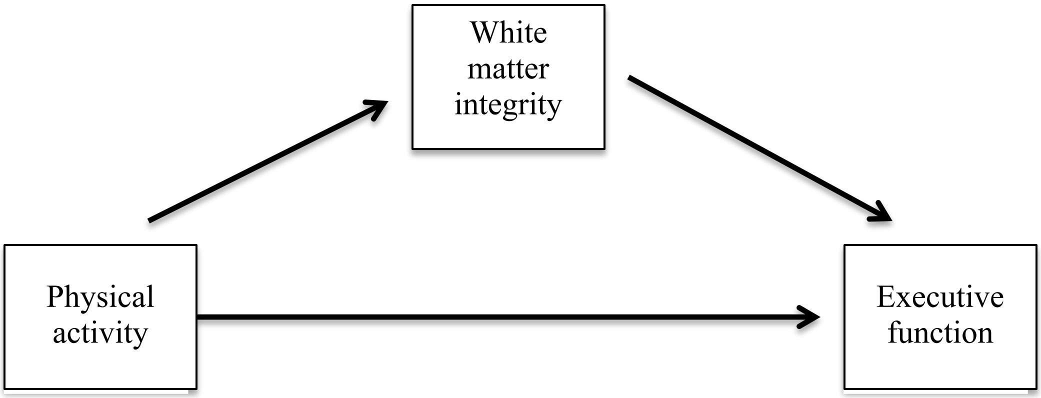


Figure 2. Proposed model of the relations between physical activity, executive function, and white matter integrity.

CHAPTER 2

METHOD

Participants

Participants were a total of 43 older adults, aged 65-85 years, from the surrounding community of a southeastern college town. These participants were recruited over a two-year period. Some participants' data were acquired as part of a previously completed pilot intervention study, but for the purpose of the present study, only data from their baseline assessments (pre-intervention) was used. The rest of the subjects were collected following the same data acquisition protocol as the baseline visits of the earlier study. All subjects participated in sessions that included neuropsychological testing, physical activity and fitness measurements, and magnetic resonance imaging (MRI). Participants were eligible if they had no self-reported neurological (e.g., Alzheimer's, Parkinson's) or psychiatric disorders, were right-handed, Native English speakers, and were compatible with the MRI environment (i.e., no metal implants, no recent surgeries, etc). Descriptive statistics are presented in Table 1.

Physical Activity

Physical activity was measured using NL-1000 Accelerometers (New Lifestyles, Inc.; Lee's Summit, Missouri, USA). This device is classified by its manufacturer as an accelerometer because it measures physical activity intensity, number of steps, and distance covered using a piezoelectric strain gauge. Participants in this study wore the NL-1000 on their waist for 7 days. For adults, activity intensity levels of 1 to 3 capture light activity (breathing normally), levels 4 to 6 indicate moderate activity (breathing more heavily than normal), and levels 7 to 9 are categorized as vigorous activity (huffing & puffing). Moderate/Vigorous Physical Activity

(MVPA) is a measurement of the time spent in moderate to vigorous activity and is captured when the device is set to record activity between levels 4 to 9 (NL-1000 Activity Monitor: user's guide & record book, 2005). Time spent in MVPA is broken down into 24 hour increments and the amount of time spent in MVPA is displayed in days up to day 7 on the device. These settings were used in the current study, as recommended. In the current study, MVPA was calculated as the average time in seconds per day spent in moderate to vigorous physical activity over the span of seven days using the following equation: Average MVPA = [(Total Time MVPA Day 1 + Total Time MVPA Day 2 + Total Time MVPA Day 3 + Total Time MVPA Day 4 + Total Time MVPA Day 5 + Total Time MVPA Day 6 + Total Time MVPA Day 7)/7]. MVPA as calculated by the NL-1000 has been shown to be both valid and reliable in measuring physical activity level in children and adults (Ayabe et al., 2006; McClain & Tudor-Locke, 2009). In addition, the average number of steps taken per day over the span of seven days was calculated as follows: Average Steps = [(Total Steps Day 1 + Total Steps Day 2 + Total Steps Day 3 + Total Steps Day 4 + Total Steps Day 5 + Total Steps Day 6 + Total Steps Day 7)/7].

Executive Function

Each participant received neuropsychological testing by a trained graduate student. All participants were administered the Delis-Kaplan Executive Function System (DKEFS) Color-Word Inference Test, the DKEFS Verbal Fluency Test, and the DKEFS Trail Making Test, which are subtests of the full DKEFS battery. The DKEFS Trail-making Test, Verbal Fluency, and Color Word Inference were chosen because they have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times (Delis et al., 2004). For the Trail Making Test, a scaled score was calculated for Condition 4: Number-Letter Switching, which measures the ability to set-shift. For Verbal Fluency, a scaled score for Category Switching was calculated, which measures the ability to generate words that fall under categories while being able to set-shift. For the Color-Word Inference Test, a scaled score was calculated for Condition 4: Inhibition/Switching, which measures verbal inhibition and set-shifting (D-KEFS; Delis, Kaplan, & Kramer, 2001). Scaled scores were then averaged together for each participant to create an executive function composite score. In order to determine whether these three measures are correlated with each other and are thus measuring similar constructs, a Cronbach's alpha based on standardized items (Bland, 1997) was calculated (α=.600) indicating acceptable fit for the composite (Hinton, et al., 2004), given the small number of items.

Imaging Acquisition

Neuroimaging scans were acquired using a General Electric Signa HDx 3T MRI (GE; Waukesha, WI). A high-resolution 3D T1-weighted fast spoiled gradient recalled (FSPGR) sequence was used to collect structural scans (TE = < 5 ms; TR = 7.5 ms; flip angle = 20°; 154 axial slices; slice thickness = 1.2 mm; FOV = 256 × 256 mm matrix). Total acquisition time for these images was 6 minutes, 20 seconds.

Diffusion weighted imaging (DWI) scans were acquired using a single-shot diffusion-weighted spin-echo sequence (SE-EPI) (TE = <5 ms, TR = 15900 ms, 90° flip angle, 60 interleaved slices, slice gap = 0 mm, 2 mm isotropic voxels, acquisition matrix = 128 x 128, FOV = 256 x 256 mm, parallel acceleration factor = 2, b-value: 1000, and 30 optimized gradient directions with 3 b0 images). Total scan time for the DTI acquisition was 9 minutes, 38 seconds.

Additionally, two pairs of magnitude and phase images were acquired for fieldmap-based unwarping of DWIs to correct for artifacts (Soares et al., 2013) (TE1 = < 5.0 ms and TE2 = 7.2ms, TR = 700 ms, 60 slices, slice gap = 0 mm, 2 mm isotropic voxels, acquisition matrix = 128 x 128, and FOV = 256 x 256 mm). Acquisition for each pair of images took 2 minutes, 20 seconds. Several other scan sequences were collected but were not relevant to the current investigation. Total scan time was approximately 75 minutes.

Image Processing

DWI images were pre-processed using the FMRIB Diffusion Toolbox (FDT; Behrens et al., 2003) following a standard pipeline. Images were corrected for head motion and eddy current distortions using the eddy current and motion correction tool, with the first b0 image as a reference. Next, brain extraction was accomplished using the brain extraction tool (BET; Smith, 2002). Distortions to DWIs were corrected using fieldmaps calculated from magnitude and phase images. The tool DTFIT from the FMRIB Diffusion Toolbox was used to estimate diffusion tensors for each voxel.

Following the pre-processing steps, Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), a tool within FSL (Smith et. al., 2004) was used to create mean FA, AD, RD, and MD images. TBSS also addresses issues with decisions about spatial smoothing that can impact results such as issues with inadequate registration of participant data into a common space and optimizes this co-registration by registering every participant’s data to every other participant’s data and selecting the participant with the minimum mean displacement relative to the rest of the sample (Smith et al., 2006). After the identification of the most representative participant, all other participant’s images were transformed into standard space by aligning them with the target participant’s image and affine transforming the entire group into MNI152 standard space using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a; Andersson, Jenkinson, & Smith, 2007b). A mean FA image was created and thinned to make a mean FA skeleton, which represents the center of the white matter tracts that were common to all participants. This same procedure was then used to analyze AD, RD, and MD maps and skeletons.

Following this processing the Johns Hopkins University (JHU) ICBM-DTI-81 White Matter Atlas (Hua et al., 2008; Mori et al., 2008) was used to label sections of FA, AD, RD and MD white matter tracts in both hemispheres. A binary mask was created for each ROI (corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, cingulum, and fornix) and was used to extract the average FA, AD, RD, and MD value from each ROI. The left and right hemispheres were averaged together to create a single mean value for each ROI. These steps were applied prior to statistical analysis.

Statistical Analysis

Data was analyzed using the Statistical Package for Social Sciences (IBM SPSS Version 21.0) PROCESS Macro (Hayes, 2012). The relation between the amount of moderate to vigorous physical activity and executive function as mediated through the ROIs was examined in parallel mediation models delineated by diffusion parameter. All indirect effects were analyzed using bootstrap analyses set at 10,000 samples and a 95% confidence interval (Preacher & Hayes, 2004). In order to capture the unique relations between physical activity, executive function, and brain integrity, age was controlled for in all analyses, as age has been shown to be related to both cognitive function and the integrity of the brain (Peters, 2006).

Exploratory Analysis

Whole-brain voxelwise mediation was undertaken as an exploratory analysis, given the limited prior research available on this method. The mediation model, including the indirect relations between physical activity and executive function as mediated by white matter integrity in whole brain FA was examined using Threshold Free Cluster Enhancement and Cortex-wise Mediation (TFCE_mediation; https://github.com/trislett/TFCE_mediation), a toolbox that allows voxelwise mediation analysis of white matter tracts using any four-dimensional NifTi volume and its binary mask. A 4D NifTi volume for the skeletonized FA images for all subjects and a mean skeletonized FA mask was utilized. The effects of age on MVPA and on executive function were removed via regression and the resulting residuals were used in analysis. The resulting mediation between MVPA and executive function through whole brain FA was analyzed, with age regressed out of the 4D image. Permutation testing using parallel processing was run using 10,000 permutations. A Family-Wise Error correction rate was then applied to the maximum TFCE value among all voxels of the entire cortex for each permutation. The results were then extracted and viewed in a table at the .05 significance level and were visually inspected using FSLView (.95-1.00 threshold). A TFCE framework enhances differences in diffusivity by using study specific information instead of an unnecessarily strict threshold that can lead to Type II errors (Winkler et al., 2014). TFCE_mediation has been validated in healthy adult controls as a sensitive tool to perform voxelwise mediation analysis using DWIs (Lett et al., 2017).

The associations between average steps and executive function, as mediated by white matter integrity in regions of interest (corpus callosum, uncinate fasciculus, superior longitudinal fasciculus, cingulum, and fornix) were also examined for each diffusion parameter using the methods described above for MVPA. Age was controlled for in analyses. Average steps over the span of one week is a summary measure of general activity level and has been shown to be associated with executive function in older adults (Calamia et al., 2018). Average steps captures an overall summary measure of activity, and provides additional information beyond engagement in moderate to vigorous physical activity as measured by MVPA.

Power Analysis

Using previous literature on relative effect sizes when examining the relations between physical activity and executive function in older adults (Kerr et al., 2013) and the relations between physical activity and white matter integrity (Tian et al., 2014) a power analysis was conducted *a priori* using GPower (Erdfelder, Faul, & Buchner, 1996). The relations between time spent in moderate to vigorous physical activity as measured by one week of wearing an accelerometer and executive function as measured by the Trail Making Test in older adults ($r = 0.24$, $d=0.49$; Kerr et al., 2013) was a medium effect. The relations between self-reported level of physical activity as measured by amount of time spent in light physical activity (i.e., walking) and subsequent white matter integrity in older adults in temporal brain regions was a large effect ($r= 0.46$, $d=1.04$; Tian et al., 2013). GPower was utilized with power ($1 - \beta$) set at 0.80 and $\alpha = .05$ using the *a priori* setting Linear Multiple Regression: Fixed model, R^2 deviation from zero with two predictors (physical activity and white matter integrity). To make a conservative estimate of the effect size based on previous research, f^2 was set at .25 ($r=0.46$) to estimate a medium effect ($f^2= R^2/1-R^2$). This analysis showed that the total sample size would have to be $N = 42$ in order to reach statistical significance at the .05 level.

CHAPTER 3

RESULTS

Primary Analyses

For the primary analyses, the association between average MVPA and executive function controlling for age did not quite reach statistical significance (t=1.772, *p*=.08). Contrary to our hypotheses, white matter integrity did not mediate the relation between average MVPA and executive function when controlling for age for any of the diffusion parameters (Tables 2-5). However, there were significant associations between certain variables in the FA, RD, and MD mediation models, but not in the AD mediation model (see Figures 3-6). In the FA mediation model, the association between MVPA and cingulum FA was significant (t=2.236, *p*=.03). In the MD mediation model, there was a significant association between corpus callosum MD and executive function controlling for average MVPA and other ROIs of the same diffusivity parameter (t=-3.380, *p*=.002). In the RD mediation model, there was a significant association between corpus callosum RD and executive function controlling for average MVPA and other ROIs of the same diffusivity parameter (t=-2.277, *p*=.029). These associations between variables in the FA, MD, and RD models were all in the expected directions given the hypotheses.

Exploratory Analyses

Results obtained from TFCE_mediation indicated that no whole brain FA clusters significantly mediated the association between average MVPA and executive function at the $p \leq .05$ level. (Figure 11).

The association between average steps and executive function when controlling for age was significant (t=2.829, *p*=.007). However, white matter integrity did not mediate this association when controlling for age for any of the diffusion parameters (Tables 6-9). There were significant associations between variables in the FA, MD, RD, and AD mediation models (see Figures 7-10). In the FA mediation model, average steps was significantly associated with cingulum FA (t=3.463 *p*=.001) and superior longitudinal fasciculus FA (t=2.11, *p*=.04). In the MD mediation model, there was a significant association between the corpus callosum MD and executive function, controlling for average steps and other MD ROIs (t=-3.346, *p*=.002). The association between average steps and executive function controlling for the MD ROIs was also significant (t=2.533, *p*=.016). In the RD mediation model, there was a significant association between average MVPA and superior longitudinal fasciculus RD (t=-2.073, *p*=.04), as well as MVPA and cingulum RD (t=-2.997, *p*=.005). There was a significant association between corpus callosum RD and executive function, controlling for average steps and other RD ROIs (t=-2.254, *p*=.03). All of these associations were in the hypothesized directions. In the AD mediation model, the association between average steps and executive function controlling for the AD ROIs was also significant (t=2.300, *p*=.028).

Table 2. Multiple mediation results for the relations between average moderate to vigorous physical activity (MVPA), executive function, and FA regions of interest controlling for age.

Variable	β	CI	t	*p*
Average MVPA to Mediators				
Corpus Callosum	.0547	[-.0734, .1827]	.8631	.39
Uncinate Fasciculus	.1596	[-.0211, .3404]	1.785	.08
Superior Longitudinal Fasiculus	.0839	[-.0318, .1996]	1.466	.15
Cingulum	.1559	[.0149, .2969]	2.236	.03*
Fornix	.0281	[-.2634, .3197]	.1951	.85
Direct Effect of Mediators on Executive Function				
Corpus Callosum	.0020	[-.0073, .0047]	1.500	.14
Uncinate Fasciculus	.0004	[-.0013, .0020]	.4665	.64
Superior Longitudinal Fasiculus	-.0001	[-.0034, .0031]	-.0820	.94
Cingulum	.0002	[-.0007, .0012]	.1424	.89
Fornix	.0003	[-.0007, .0012]	.5579	.58
Total Effect MVPA	.0007	[-.0001, .0014]	1.772	.08
Remaining Direct Effect MVPA	.0005	[-.0003, .0013]	1.213	.23
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.0001	.0002	-.0002	.0006
Uncinate Fasciculus	.0001	.0002	-.0002	.0006
Superior Longitudinal Fasiculus	-.00001	.0003	-.0006	.0005
Cingulum	.00003	.0002	-.0004	.0005
Fornix	.00001	.0001	-.0002	.0002
Total Indirect Effect	.0002	.0003	-.0004	.0007

*denotes p<.05

Table 3. Multiple mediation results for the relations between average moderate to vigorous physical activity (MVPA), executive function, and MD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average MVPA to Mediators				
Corpus Callosum	-.00002	[-.0001, .0001]	-.3616	.72
Uncinate Fasciculus	-.0001	[-.0002, .0001]	-.9793	.33
Superior Longitudinal Fasiculus	-.0001	[-.0002, .0001]	-1.008	.32
Cingulum	-.00003	[-.0001, .0001]	-.6653	.51
Fornix	.00001	[-.0013, .0013]	.0178	.99
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-4.2062	[-6.732, -1.680]	-3.380	.002**
Uncinate Fasciculus	.8072	[-1.429. -3.043]	.7328	.47
Superior Longitudinal Fasiculus	.5577	[-1.979, 3.094]	.4463	.66
Cingulum	.1552	[-2.747, 3.057]	.1086	.91
Fornix	.0193	[-.0329, .2835]	.2102	.84
Total Effect MVPA	.0007	[-.0001, .0014]	1.772	.08
Remaining Direct Effect MVPA	.0007	[-.00003, .0014]	1.938	.06
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.0001	.0002	-.0003	.0007
Uncinate Fasciculus	-.00004	.0001	-.0004	.0001
Superior Longitudinal Fasiculus	-.00003	.0001	-.0004	.0002
Cingulum	-.00001	.0001	-.0002	.0002
Fornix	.0000002	.0001	-.0001	.0002
Total Indirect Effect	.000003	.0002	-.0005	.0005

*denotes *p*<.05, ***p*<.01

Table 4. Multiple mediation results for the relations between average moderate to vigorous physical activity (MVPA), executive function, and RD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average MVPA to Mediators				
Corpus Callosum	-.0001	[-.0002, .0001]	-.7042	.49
Uncinate Fasciculus	-.0001	[-.0003, .00004]	-1.562	.13
Superior Longitudinal Fasiculus	-.0001	[-.0002, .00004]	-1.357	.18
Cingulum	-.0001	[-.0002, .000004]	-1.943	.059
Fornix	.00001	[-.0014, .0014]	.0469	.99
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-2.305	[-4.3510, -.2503]	-2.277	.029*
Uncinate Fasciculus	-.0624	[-1.6996, 1.5747]	-.0774	.94
Superior Longitudinal Fasiculus	.6928	[-1.7194, 3.1049]	.5830	.56
Cingulum	-.3842	[-2.9020, 2.1337]	-.3097	.76
Fornix	.0002	[-.1832, .1837]	.0026	.998
Total Effect MVPA	.0007	[-.0001, .0014]	1.772	.08
Remaining Direct Effect MVPA	.0005	[-.0002, .0013]	1.448	.16
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.0001	.0002	-.0002	.0007
Uncinate Fasciculus	.00001	.0002	-.0003	.0004
Superior Longitudinal Fasiculus	-.0001	.0002	-.0007	.0003
Cingulum	.00004	.0002	-.0003	.0005
Fornix	.00000	.0002	-.0001	.0001
Total Indirect Effect	.0001	.0002	-.0004	.0006

*denotes $p<.05$

Table 5. Multiple mediation results for the relations between average moderate to vigorous physical activity (MVPA), executive function, and AD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average MVPA to Mediators				
Corpus Callosum	.0001	[-.0001, .0002]	.6827	.50
Uncinate Fasciculus	.0001	[-.0001, .0003]	1.076	.29
Superior Longitudinal Fasiculus	.000002	[-.0002, .0002]	.0207	.98
Cingulum	.0001	[-.0001, .0004]	1.259	.22
Fornix	.00001	[-.0012, .0011]	.0239	.98
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-1.336	[-3.133, .4617]	-1.509	.14
Uncinate Fasciculus	1.224	[-.2960, 2.7448]	1.635	.11
Superior Longitudinal Fasiculus	-1.271	[-3.3819, .8398]	-1.222	.23
Cingulum	.8633	[-.7141, 2.4408]	1.111	.27
Fornix	-.0818	[-.3423, .1768]	-.6375	.53
Total Effect MVPA	.0007	[-.0001, .0014]	1.772	.08
Remaining Direct Effect MVPA	.0005	[-.0003, .0013]	1.285	.21
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	-.0001	.0001	-.0004	.0001
Uncinate Fasciculus	.0001	.0002	-.0001	.0005
Superior Longitudinal Fasiculus	-.000002	.0001	-.0003	.0002
Cingulum	.0001	.0002	-.0001	.0006
Fornix	-.000001	.0001	-.0002	.0001
Total Indirect Effect	.0002	.0002	-.0002	.0007

Table 6. Multiple mediation results for the relations between average steps, executive function, and FA regions of interest controlling for age.

Variable	β	CI	t	*p*
Average Steps to Mediators				
Corpus Callosum	.0354	[-.0021, .0729]	1.907	.06
Uncinate Fasciculus	.0465	[-.0084, .1015]	1.711	.09
Superior Longitudinal Fasiculus	.0357	[.0016, .06968]	2.115	.04*
Cingulum	.0681	[.0284, .1079]	3.463	.001**
Fornix	.0546	[-.0320, .1413]	1.274	.21
Direct Effect of Mediators on Executive Function				
Corpus Callosum	.0019	[-.0007, .0045]	1.458	.15
Uncinate Fasciculus	.0004	[-.0011, .0021]	.5949	.56
Superior Longitudinal Fasiculus	-.0001	[-.0033, .0030]	-.0846	.93
Cingulum	-.0002	[-.0027, .0023]	-.1776	.86
Fornix	.0002	[-.0007, .0011]	.4503	.66
Total Effect Average Steps	.0003	[.0001, .0005]	2.8287	.007**
Remaining Direct Effect Average Steps	.0002	[-.00002, .0005]	1.8501	.07
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.00007	.0001	-.0001	.0002
Uncinate Fasciculus	.00002	.0001	-.0001	.0001
Superior Longitudinal Fasiculus	-.000004	.00005	-.0002	.0002
Cingulum	-.00001	.0001	-.0002	.0002
Fornix	.00001	.0001	-.00004	.0001
Total Indirect Effect	.00008	.00002	-.0001	.0003

*denotes *p*<.05, ***p*<.01

Table 7. Multiple mediation results for the relations between average steps, executive function, and MD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average Steps to Mediators				
Corpus Callosum	-.00003	[-.0001, .00001]	-1.513	.14
Uncinate Fasciculus	-.00003	[-.0001, .000003]	-1.855	.07
Superior Longitudinal Fasiculus	-.00003	[-.0001, .00001]	-1.728	.09
Cingulum	-.00002	[-.00005, .00002]	-.9795	.33
Fornix	-.0002	[-.0006, .0002]	-1.160	.25
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-4.0172	[-6.4545, -1.5799]	-3.346	.002**
Uncinate Fasciculus	1.0636	[-1.1216, 3.2487]	.9881	.33
Superior Longitudinal Fasiculus	.6718	[-1.7861, 3.1297]	.5549	.58
Cingulum	.0391	[-2.7708, 2.8491]	.0283	.98
Fornix	.0513	[-.1312, .2337]	.5705	.57
Total Effect Average Steps	.0003	[.0001, .0005]	2.829	.007**
Remaining Direct Effect Average Steps	.0003	[.0001, .0005]	2.533	.016*
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.0001	.0001	-.00002	.0003
Uncinate Fasciculus	-.00003	.0001	-.0002	.00003
Superior Longitudinal Fasiculus	-.00002	.0001	-.0002	.0001
Cingulum	-.000001	.00004	-.0001	.0001
Fornix	-.00001	.00003	-.0001	.00004
Total Indirect Effect	.00004	.0001	-.0001	.0002

*denotes *p*<.05, ***p*<.01

Table 8. Multiple mediation results for the relations between average steps, executive function, and RD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average Steps to Mediators				
Corpus Callosum	-.00005	[-.0001, .000004]	-1.872	.07
Uncinate Fasciculus	-.0001	[-.0001, .000004]	-1.883	.07
Superior Longitudinal Fasiculus	-.00004	[-.0001, -.000001]	-2.073	.04*
Cingulum	-.0001	[-.0001, -.00002]	-2.997	.005**
Fornix	-.0002	[-.0064, .0002]	-1.162	.25
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-2.212	[-4.204, -.2197]	-2.254	.03*
Uncinate Fasciculus	-.0487	[-1.644, 1.546]	-.0620	.95
Superior Longitudinal Fasiculus	.6840	[-1.669, 3.037]	.5901	.56
Cingulum	-.0945	[-2.594, 2.404]	-.0772	.94
Fornix	.0258	[-.1556, .2072]	.2888	.77
Total Effect Average Steps	.0003	[.0001, .0005]	2.829	.007**
Remaining Direct Effect Average Steps	.0002	[-.0001, .0005]	1.978	.06
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	.0001	.0001	-.00004	.0003
Uncinate Fasciculus	.00002	.00005	-.0001	.0001
Superior Longitudinal Fasiculus	-.00003	.0001	-.0002	.0001
Cingulum	.00001	.0001	-.0002	.0002
Fornix	-.00001	.00003	-.0001	.00005
Total Indirect Effect	.0001	.0001	-.0001	.0002

*denotes $p<.05$, **$p<.01$

Table 9. Multiple mediation results for the relations between average steps, executive function, and AD regions of interest controlling for age.

Variable	β	CI	t	*p*
Average Steps to Mediators				
Corpus Callosum	.00001	[-.00004, .0001]	.5151	.61
Uncinate Fasciculus	.000002	[-.0001, .0001]	.0653	.95
Superior Longitudinal Fasiculus	-.00001	[-.0001, .00004]	-.4246	.67
Cingulum	.0001	[-.000005, .0001]	1.874	.07
Fornix	-.0002	[-.0005, .0001]	-1.132	.26
Direct Effect of Mediators on Executive Function				
Corpus Callosum	-1.259	[-2.975, .4567]	-1.490	.15
Uncinate Fasciculus	1.317	[-.1172, 2.752]	1.864	.07
Superior Longitudinal Fasiculus	-.8710	[-2.930, 1.188]	-.8588	.40
Cingulum	.4545	[-1.114, 2.023]	.5881	.56
Fornix	-.0670	[-.3155, 1.1815]	-.5474	.59
Total Effect Average Steps	.0003	[.0001, .0005]	2.8287	.007**
Remaining Direct Effect Average Steps	.0003	[.00003, .0005]	2.300	.028*
Indirect effect-Bootstrap results	β	SE	LLCI	ULCI
Corpus Callosum	-.00002	.00003	-.0001	.0001
Uncinate Fasciculus	.000002	.00004	-.0001	.0001
Superior Longitudinal Fasiculus	.00001	.00003	-.0001	.0001
Cingulum	.00003	.0001	-.0001	.0002
Fornix	.00001	.00003	-.00003	.0001
Total Indirect Effect	.00004	.0001	-.0001	.0002

*denotes $p<.05$, **$p<.01$

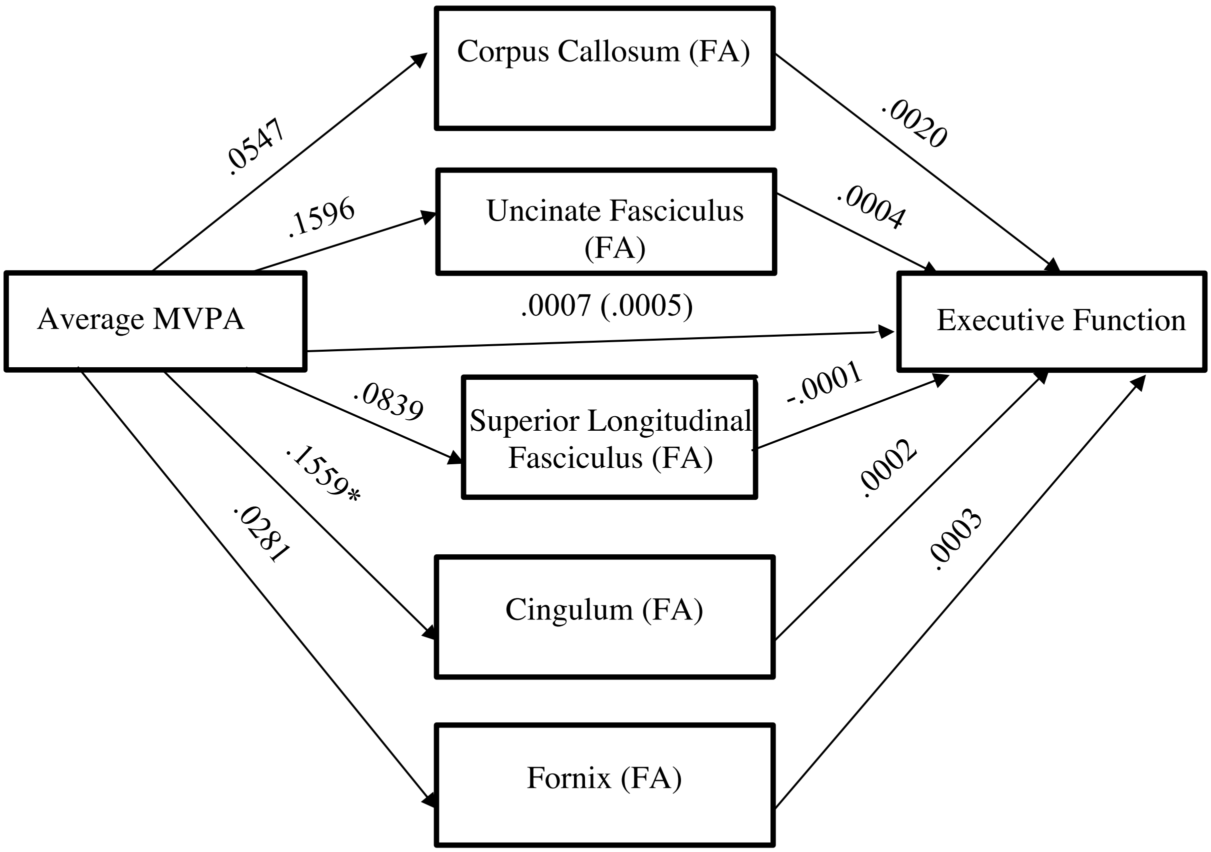


Figure 3. Mediation model for the correlations between average moderate to vigorous physical activity (MVPA), executive function, and FA regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between Average MVPA and executive function controlling for each of the ROIs in parantheses. *$p < .05$

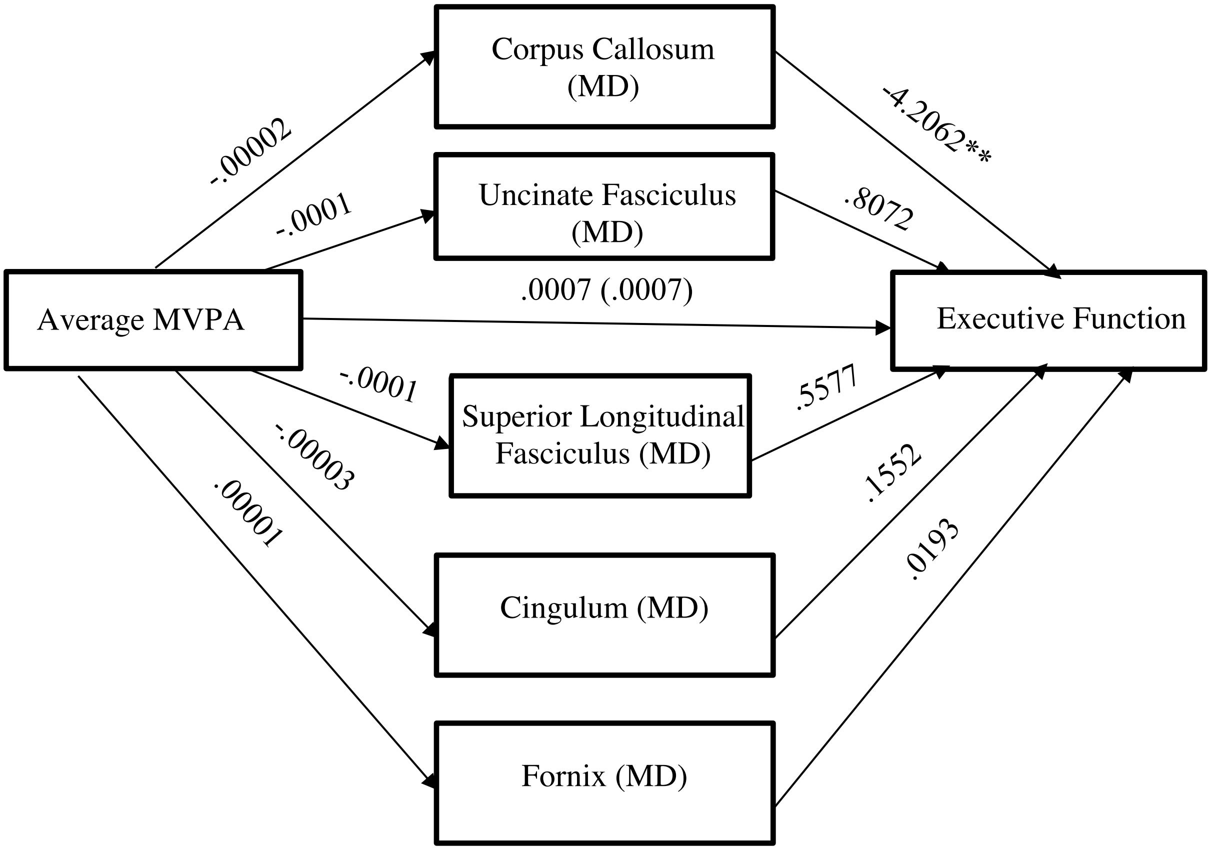


Figure 4. Mediation model for the relations between average moderate to vigorous physical activity (MVPA), executive function, and MD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between Average MVPA and executive function controlling for each of the ROIs in parantheses. *p<.05, **p<.01

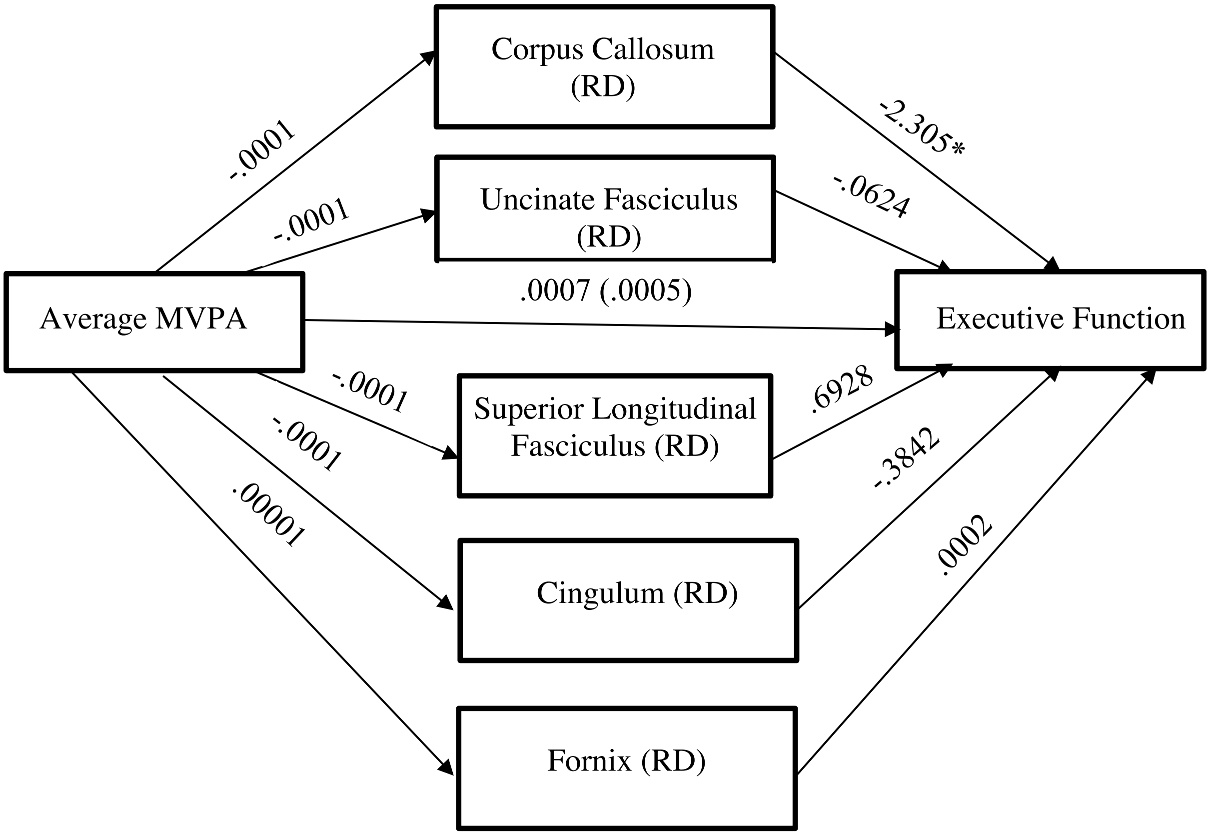


Figure 5. Mediation model for the relations between average moderate to vigorous physical activity (MVPA), executive function, and RD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between Average MVPA and executive function controlling for each of the ROIs in parantheses. *p<.05

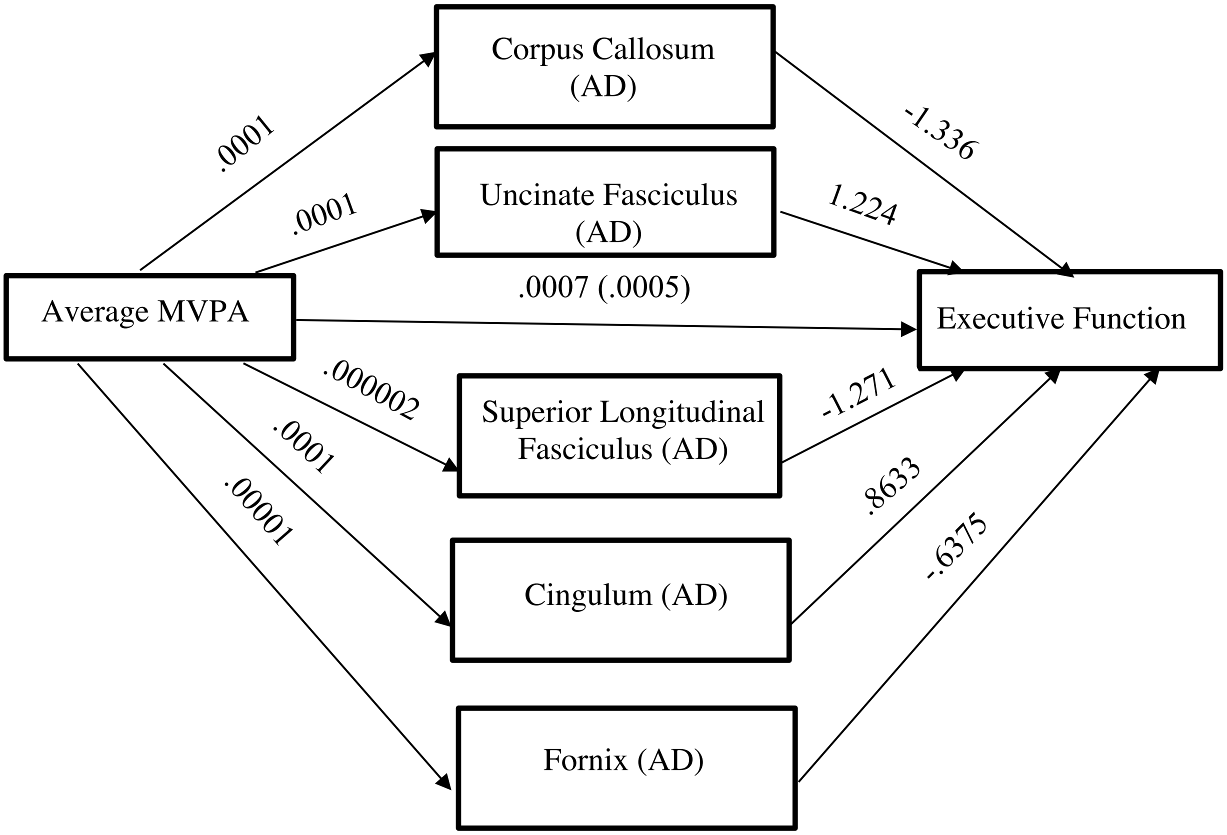


Figure 6. Mediation model for the relations between average moderate to vigorous physical activity (MVPA), executive function, and AD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between Average MVPA and executive function controlling for each of the ROIs in parantheses.

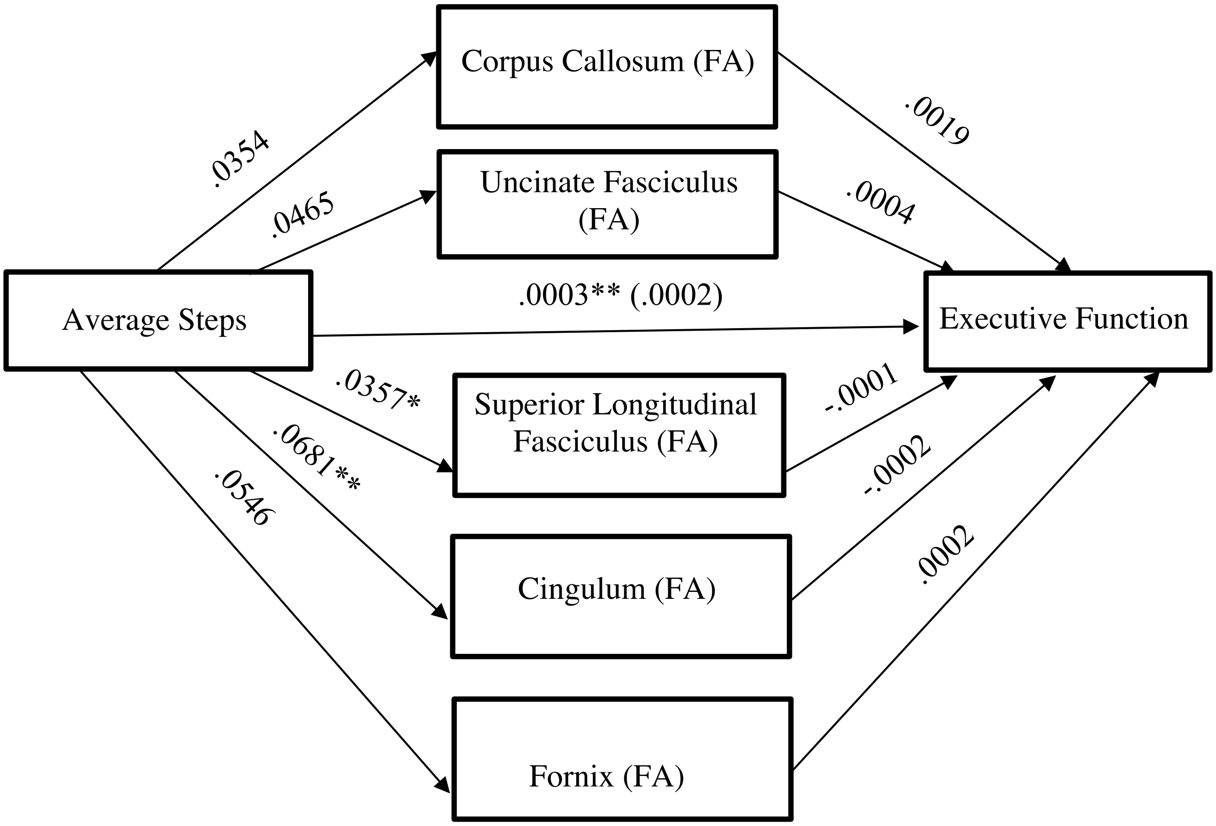


Figure 7. Mediation model for the relations between average steps, executive function, and FA regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between average steps and executive function controlling for each of the ROIs in parantheses.
*p<.05, **p<.01

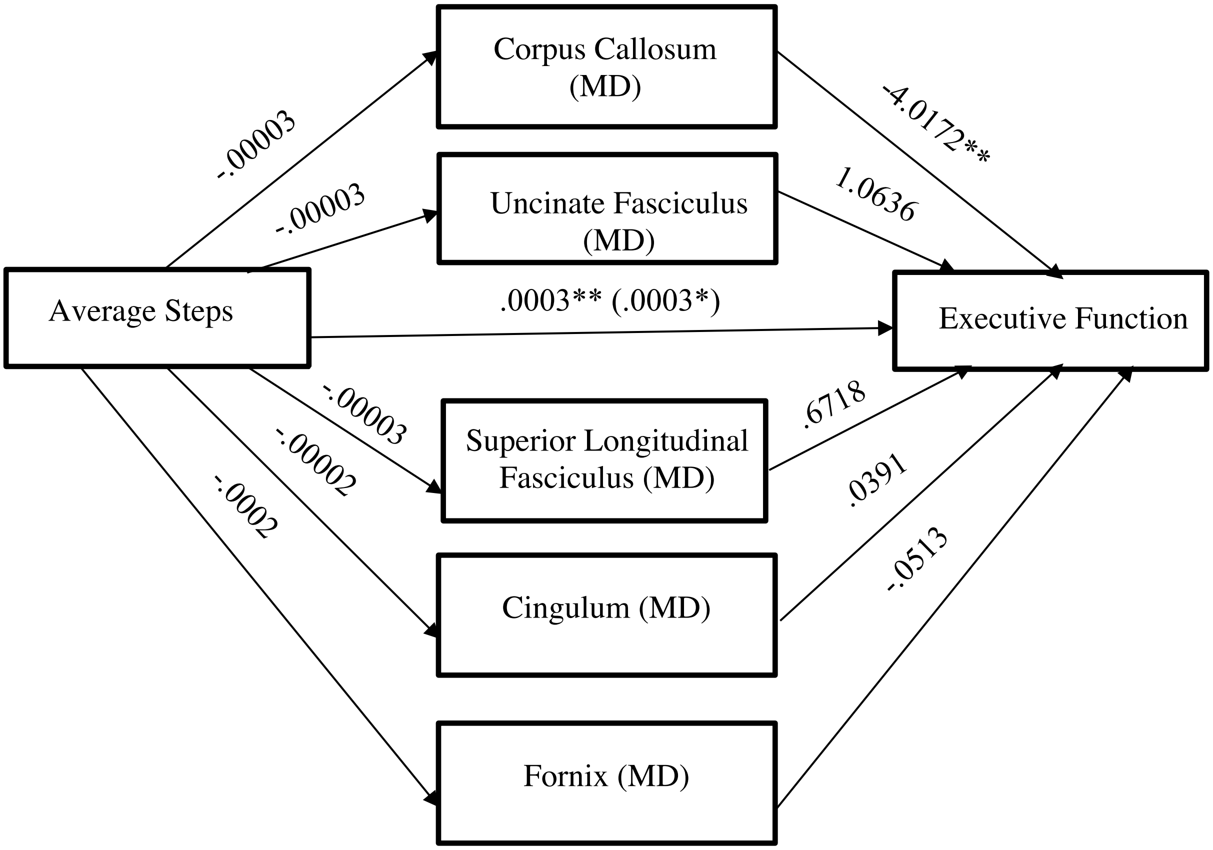


Figure 8. Mediation model for the relations between average steps, executive function, and MD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between average steps and executive function controlling for each of the ROIs in parantheses.
**p*<.05, ***p*<.01

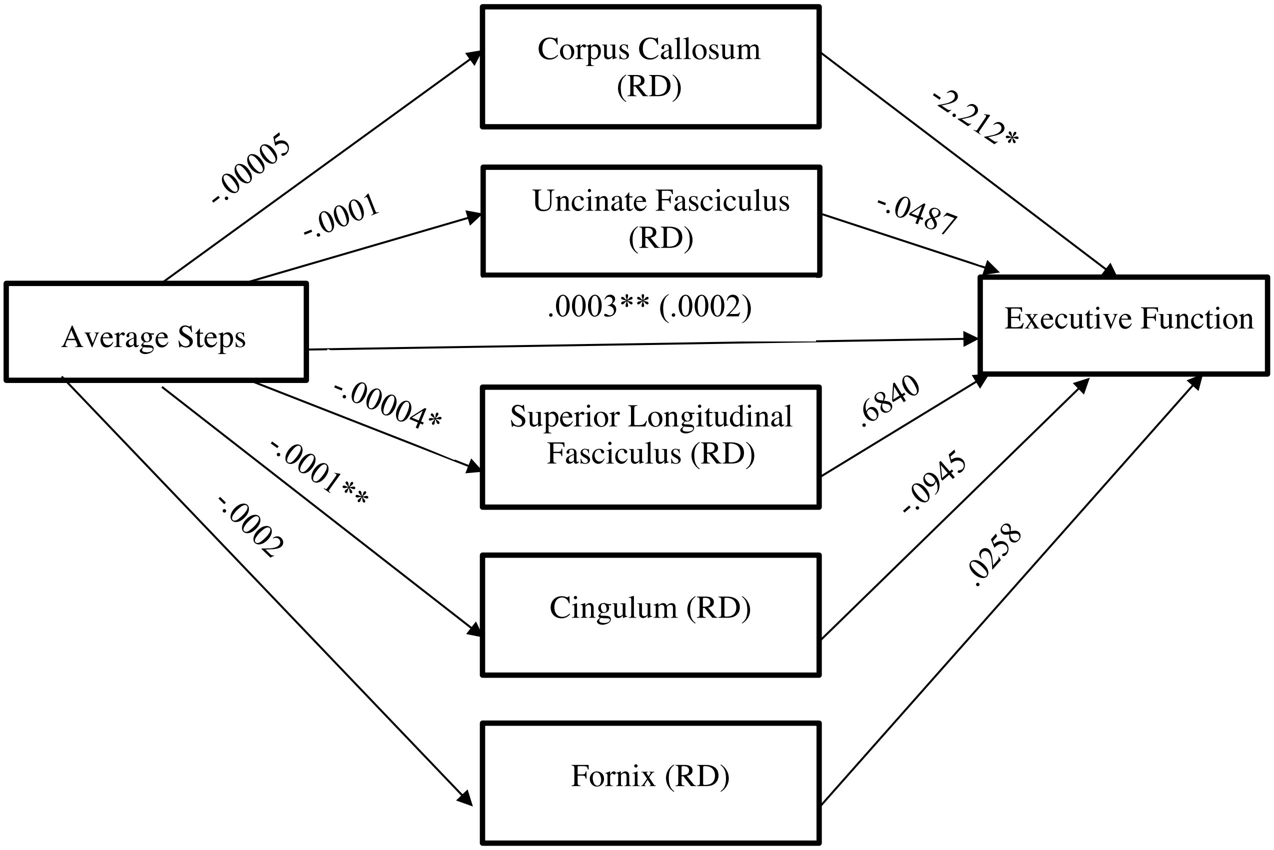


Figure 9. Mediation model for the relations between average steps, executive function, and RD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between average steps and executive function controlling for each of the ROIs in parantheses.
*$p<.05$, **$p<.01$

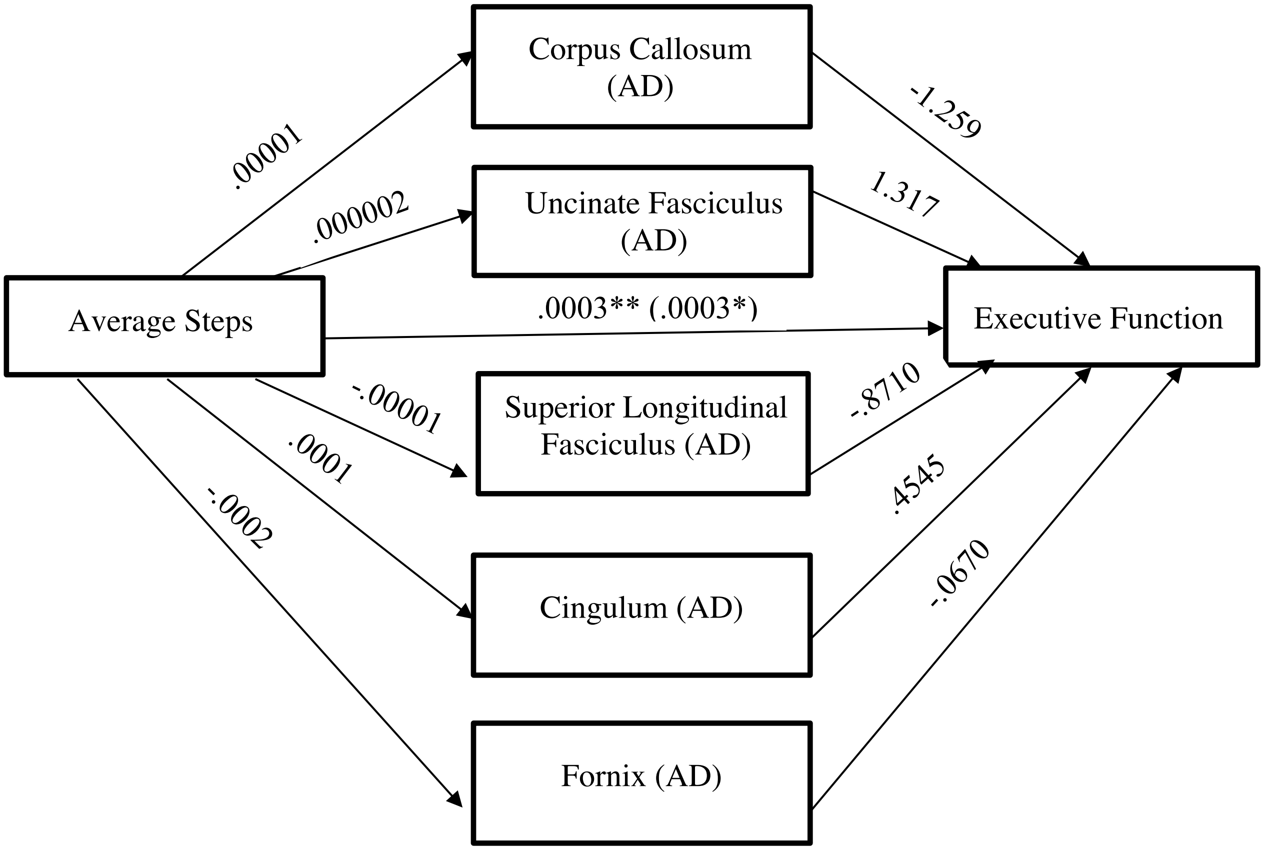


Figure 10. Mediation model for the relations between average steps, executive function, and AD regions of interest controlling for age. The standardized regression coefficients are presented, with the standardized regression coefficient between average steps and executive function controlling for each of the ROIs in parantheses.
**p*<.05, ***p*<.01

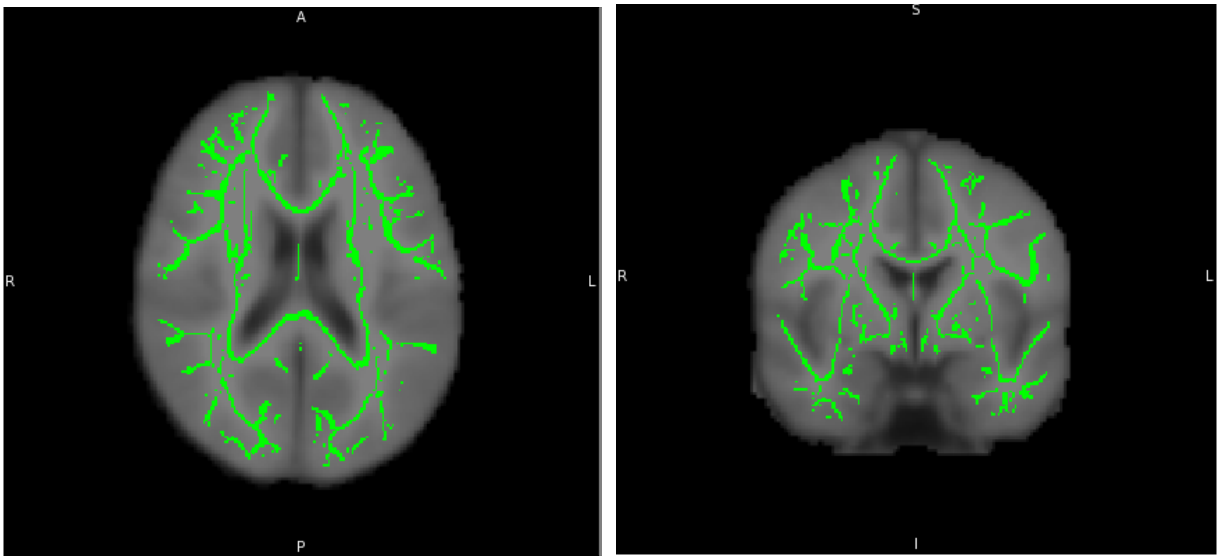


Figure 11. Whole brain white matter FA does not mediate the association between MVPA and executive function. This image was viewed in FSLView and illustrates the mean FA skeleton mask in green (.2-.7 threshold) overlaid on the all subjects FA images and the MNI152 template. The 1-P_{FWE} mediation image does not survive thresholding at .95 and is not pictured. Images are shown in the axial and coronal view.

CHAPTER 4

DISCUSSION

In this study, our primary aim was to assess whether white matter integrity mediated the relation between physical activity, as measured by MVPA, and executive function in a sample of older adults using diffusion tensor imaging (DTI). Contrary to our expectations, we found that white matter integrity did not mediate this relation as measured by any of the examined diffusivity measures. While nearing significance, we found that MVPA was not significantly related to executive function in our sample. However, there were several variables within the mediation models that were significantly associated. MVPA and cingulum FA were significantly positively associated, indicating that increased MVPA was related to greater preservation of axonal myelin sheaths in the cingulum. The cingulum is a large, heterogeneous white matter tract that spans and connects frontal, temporal, and medial parietal areas and is implicated in attention and executive function, learning, and episodic memory (Bubb, Metzler-Baddeley & Aggleton, 2018). Therefore, the significant positive association between the preserved integrity of axonal myelin sheaths in the cingulum and MVPA in our sample suggests that older adults who engage in more moderate to vigorous physical activity have preserved brain integrity in the cingulum, which is important for many activities of daily that older adults would need to engage in. Additionally, corpus callosum MD and RD were significantly negatively associated with executive function (controlling for average MVPA and other ROIs of the same diffusivity parameter). This indicates that better executive function ability was significantly related to preserved axons and myelination of the corpus callosum. These results are in line with literature supporting the role of corpus callosum white matter integrity in shifting/inhibition aspects of executive function in older adults (Bettcher et al., 2016), and suggest that better executive functioning was related to preserved integrity of the corpus callosum in our sample. We hypothesized that it was possible that by analyzing the mediation using a single mean value to define the diffusivity parameter of each tract, the possibility to pick up on changes in specific regions of the ROI was eliminated. Given that differences have been found in diffusivity in the aging brain when white matter integrity is examined globally versus specifically in a voxel-wise manner (de Groot, 2015), we decided to address this issue in exploratory whole brain TFCE_mediation analyses of FA. However, we found that none of the FA clusters significantly mediated the association between average MVPA and executive function.

When examining the relations between average steps and executive function as mediated by white matter integrity, there was a significant positive association between average steps and executive function, and this association remained significant even when controlling for mediators in the MD and AD mediation models. This is in line with research indicating that older adults that simply move around more during the day display better executive function compared to older adults who are more sedentary (Barnes et al., 2008), likely due to increased environmental stimulation (e.g., social activities, encountering cognitively challenging experiences). Additionally, it is possible that higher intensity physical activity is not necessarily better than just engaging in any physical activity, and this is why we found that more steps was significantly associated with better executive function in our sample while MVPA was not. A recent comparison of high intensity interval training, moderate continuous aerobic training, and resistance training on executive function in older adults found significant changes in executive function for moderate continuous aerobic training, and resistance training, but not for high intensity interval training, which the authors suggested may be in line with evidence that neurocognitive networks are differentially impacted by mode of exercise (Coetsee & Terblanche, 2017). This is similar to our results showing that MVPA was not significantly associated with executive function, while steps, a less intense and more global measure of physical activity as compared to MVPA, was significantly associated. In addition to a significant direct effect, there were also several variables within these mediation models that were significantly associated. Similar to the MVPA associations listed above, average steps was significantly associated with cingulum FA and additionally cingulum RD integrity, indicating that greater amount of steps was significantly associated with greater preservation of axonal myelin sheaths and overall myelination in the cingulum. In addition, average steps was also significantly associated with superior longitudinal fasciculus FA and RD integrity, suggesting that taking more steps throughout the day is associated with greater preservation of axonal myelin sheaths and overall myelination in the superior longitudinal fasciculus. This is in line with research that has found that the associations between steps and white matter integrity in older adults is strongest in the superior longitudinal fasciculus (Tian et al., 2015), which has been implicated in information processing speed. Information processing speed is a cognitive domain that has been shown to be positively impacted by physical activity and exercise interventions (Dustman, Emmerson & Shearer , 1994). Finally, corpus callosum MD and RD integrity were significantly associated with better executive function (controlling for average steps and other ROIs of the same diffusivity parameter), indicating that better executive function ability was significantly related to preserved axons and overall myelination of the corpus callosum. This finding follows the same pattern as the MVPA analyses above.

There are several possible explanations for failing to find white matter integrity as a significant mediator between physical activity measures and executive function in older adults. The participants in this study were relatively independent, community-dwelling, and highly educated individuals who performed in the average range on our standardized measure of executive function (Table 1). It is likely that this mediation may not exist in a sample of older adults that are relatively high-functioning. It would be important to discern whether white matter integrity mediates this relation in a group of older adults with a wider range of executive function abilities and white matter structural integrity. Additionally, there is evidence from a recent meta-analysis that older adults who are given an accelerometer, even without an intervention, engage in more physical activity (Cooper et al., 2018). Therefore, physical activity measured via accelerometer may be an overestimation of the regular amount of physical activity in a typical week. In addition, it is possible that one week of accelerometer wear may not be an accurate reflection of the lifetime physical activity of an older adult given the possibilities for interference from outside factors (e.g., weather, sickness/illness, schedule of activities for that particular week). Future studies should monitor physical activity over a longer time span. It is also very likely that many factors that have been shown to impact physical activity, brain integrity, and executive function influenced the results of our study, but their influence was unaccounted for in our mediation models because these variables were not collected as part of the original study. For instance, cardiovascular disease risk factors (e.g., blood pressure, insulin resistance, obesity, high cholesterol, smoking) have been shown to impact both neuropsychological function and the structure of the brain (Leritz et al., 2011) but were not measured in the current study. In addition, body composition variables such as frailty (as defined by Fried et al., 2001) have been associated with decreased physical activity and cognitive performance but were also not included in the current study (Brigola et al., 2015). It is possible that these additional factors may have influenced the results in the current study, and future studies should strive to account for these variables in their mediation models.

There are several limitations to the current study. This study was cross-sectional and therefore limits the conclusions that can be drawn. Future work should utilize longitudinal methods and a larger sample to establish a clearer timeline. In addition, the restricted range of level of performance on our measure of executive functioning, lack of health and body composition factors included in the models, and proportion of highly educated and white participants somewhat limit the applicability of this study to the general population.

Despite these limitations, this study supports previous literature demonstrating a significant association between physical activity and executive function in older adults and provides novel information on associations within models examining the relations between physical activity and executive function as mediated by white matter integrity both specifically in ROIs and globally. All of the significant associations were in the expected directions and therefore can be a jumping off point for future studies interested in examining this question in a larger and more diverse sample. White matter integrity did not directly influence the relation between physical activity and executive function in older adults in our sample on its own, but future research should examine additional factors that may also contribute including additional health and fitness variables. In addition, this is one of very few studies to examine a mediation in both and a ROI analysis and a voxel-wise analysis using the new software program TFCE_mediation, which meaningfully adds to this emerging methodology.

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