APOLIPOPROTEIN E STATUS, FUNCTIONAL INDEPENDENCE, AND WHITE MATTER MICROSTRUCTURE IN OLDER ADULTS

by

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(Under the Direction of L. Stephen Miller)

ABSTRACT

The purpose of this study was to add to the literature regarding the relations between Apolipoprotein E (APOE) e4 allele, observed functional independence, as measured by instrumental activities of daily living (IADL), and white matter microstructure in older adults. Participants included 56 older adults. One-Way ANOVA revealed those with the e4 allele performed worse than e4 negative participants, $F(1,54)=4.137$, $p=.023$, one-tailed. IADL was not related to mean FA of the corona radiata ($p=.457$), corpus callosum ($p=.430$), and superior longitudinal fasciculus (SLF; $p=.229$). APOE groups did not differ in mean FA of the corona radiata ($p=.189$, one-tailed), corpus callosum ($p=.112$, one-tailed), and SLF ($p=.054$, one-tailed). Effect sizes of these differences in mean FA for these regions ranged from small to medium (Cohen's $d=.256$ - $.486$). Our findings indicate the e4 allele is related to poorer IADL when observed directly and may have a small to medium effect on white matter microstructure.

INDEX WORDS: APOE, white matter microstructure, older adults, functional independence

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THE RELATIONS BETWEEN APOLIPOPROTEIN E STATUS, FUNCTIONAL INDEPENDENCE, AND WHITE MATTER MICROSTRUCTURE IN OLDER ADULTS

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DEDICATION

This document is dedicated to my mother, Carline Jean, and my father, Rene Jean, who have helped me to see further than them by allowing me to stand on their shoulders. This document is also dedicated to my husband, Raphael Buissereth. Thank you for your continued support and for choosing to join me on this journey.

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TABLE OF CONTENTS

Page

ACKNOWLEDGEMENTS v

LIST OF TABLES vii

LIST OF FIGURES viii

CHAPTER

1 INTRODUCTION 1

APOE e2, e3, and e4 alleles 2

APOE e4 and Functional Independence 4

APOE e4 and White Matter 6

White Matter Microstructure and Functional Independence 10

Current Study 12

2 METHODS 13

Participants 13

Materials 13

Statistical Analysis 16

3 RESULTS 18

Primary Results 18

Exploratory Results 19

4 DISCUSSION 20

REFERENCES 23

LIST OF TABLES

Page

Table 1: Demographic Information and Differences by APOE status 40

LIST OF FIGURES

Page

Figure 1: Visual schematic of a diffusion tensor 39

Figure 2: Mean FA skeleton mask of participants 39

CHAPTER 1

INTRODUCTION

It is expected that by the year 2030 older adults aged 65 years and older will comprise approximately 20% of the population in the United States (Vespa, Armstrong, & Medina, 2018). According to the Congressional Budget Office, it is projected that in the next 30 years the cost for long-term services and support (LTSS) funded by taxpayers (i.e., Medicare and Medicaid) will likely nearly double (Congressional Office Budget, 2018). The proportion of individuals in older adulthood is mainly expected to increase steadily due to individuals living longer (Ortman, Velkof, & Hogan, 2014). Along with the projections of a growing older adult population comes increased risk for negative health outcomes in older adulthood (Rockwood et al., 2008; Seeman, Singer, Rowe, Horwitz, & McEwen et al., 1997). In particular, risk for neurodegenerative disorders increase as individuals age (Lyketsos & Anthony, 1999). The total estimated worldwide cost of dementia according to the 2018 World Alzheimer Report was one trillion dollars and is expected to double by the year 2030 (Patterson, 2018). It has been estimated that the cost of health care and long-term care for those with dementia in the United States is 259 billion dollars and is expected to increase four-fold by 2050 (Alzheimer's Association, 2017). Given these significant expected increases in costs related to caring for older adults with cognitive impairments, there is a growing need to understand ways to mitigate functional dependency and increase older adults' ability to live independently longer. Research suggests that healthcare costs increase as functional impairment increases. For example, Hill and colleagues (2006) found that healthcare costs reduced by $714 for every delayed impairment in

instrumental activity of daily living that was prevented by healthcare interventions within a sample of community-dwelling adults with Alzheimer's disease and other dementias (Hill, Fillit, Thomas, Chang, 2006). This has led to a growing interest in identifying factors that positively or negatively impact functional abilities in older adults.

APOE e2, e3, and e4 alleles

Apolipoprotein E (APOE) is a blood protein involved in transporting cholesterol, triglycerides, and other fats throughout the body and plays an important role in how these fats are metabolized (Huynh, Davis, Ulrich, & Holtzman, 2017, Zhao, Liu, Qiao, & Bu, 2018). There are three main types of apolipoprotein E alleles: e2, e3, and e4, which have a worldwide prevalence rate of approximately 8.4%, 77.9%, and 13.7%, respectively (Liu, Kanekiyo, Xu, & Bu, 2013). While controversial, there is some evidence to suggest the e2 allele is neuroprotective against Alzheimer's disease (AlzD) and progression from mild cognitive impairment to AlzD by increasing amyloid-beta clearance in the brain (Conejero-Goldberg, et al., 2014). The e2 allele has also been associated with reduced cardiovascular risk disease (Lopez, Krastins, & Ning, 2014). Conversely, there is evidence suggesting the e2 allele is associated with negative cerebrovascular outcomes, such as increased white matter hyperintensity load and risk of brain infarcts (Anand et al., 2009). The e3 allele is the most common allele and has generally not been related to diseases in the human population and is neither protective nor a risk factor for the development of disease (Lopez et al., 2014; Davignon, Gregg, & Sing, 1988).

The e4 allele, however, has been repeatedly found to have a negative influence on older adults' health, as it has been associated with increases in amyloid plaques (i.e., protein clumps) within the brain (Davignon et al., 1988; Caselli et al., 2010). The increase in these toxic plaques (i.e., beta amyloid plaques) in the brain can lead to neuronal death (Mahley & Rall, 2000).

Positive e4 status (i.e., carriers of the e4 allele) has been related to decreased synaptic activity, vascular function, neurogenesis, increased risk for dementia, and Alzheimer's disease (Liu et al., 2013; Slooter, et al., 1997, Liu et al., 2013; Bétard, et al., 1994). Given findings suggesting the e4 allele is less effective at transporting brain cholesterol when compared to the e3 allele, this may have significant negative consequences on central nervous system cholesterol homeostasis and neuronal health (e.g., synaptic activity, neuroplasticity; Liu et al., 2013). Regarding cognitive function in older adults, e4 carriers have been found to have worse cognitive function than those without the allele (Perna, Mons, Kliegel, & Brenner, 2016; Wisdom, Callahan, & Hawkins, 2011). E4 allele presence alongside the presence of other environmental factors (e.g., cardiovascular disease, lower education, lower literacy level) increases the risk of cognitive decline in older adults (Perna et al., 2016; Kaup et al., 2015). A meta-analysis by Wisdom and colleagues (2011) found that cognitively healthy older adults with the e4 allele exhibited worse cognitive performance on tasks related to episodic memory, executive functioning, perceptual speed, and overall global cognitive ability (Wisdom et al., 2011). Of note, e4 status has been related to Alzheimer's risk in a dose-dependent manner, with homozygotes (carrying 2 alleles) exhibiting much higher increased risk and earlier onset of AlzD than e4 heterozygotes (carrying only 1 allele; Liu et al., 2013). A review by O'Donoghue and colleagues (2018) suggest that while the effect of APOE on cognition in healthy adults is controversial, generally the presence of the e4 allele on cognition is negative and is likely due to multiple neurobiological mechanisms (e.g., reduced clearance of beta-amyloid, neuronal toxicity) which need to be further investigated (O'Donoghue, Murphy, Zamboni, Nobre, & Makay, 2018).

APOE e4 and Functional Independence

In general, older adults are at risk for experiencing modest declines in the ability to perform tasks necessary to maintain everyday activities of daily living related to functional independence as they age (Burton, Strauss, Hultsch, & Hunter, 2006; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998). The presence of the e4 allele has been related to deficits in functional independence, measured broadly, in older adults. For instance, positive e4 status was related to poorer scores on measures of self and collateral reported functional ability in a healthy older adult population, even when controlling for cognitive function (Albert et al., 1995). Verghese and colleagues (2013) found that male carriers of the e4 allele had decreased abilities in proxy measures of functional independence such as balance and gait (Verghese et al., 2013). On a composite measure of functional fitness status that included a performance based measure of basic activities of daily living (BADLs; e.g., grooming, bathing) and a six-minute walking task, researchers found that individuals with the e4 allele were more likely to be considered impaired and functionally limited (Snejdrlova et al., 2011). Melzer and colleagues (2005) found that healthy older adults with the e4 allele reported more difficulties on a chair stand task and in gait walking which have both been used as proxy measures of functional independence (Melzer, Dik, Van Kamp, Joker, & Deeg, 2005).

Research has largely found that the e4 allele is a risk factor for a host of health conditions that are related to functional status and independence (Fried, Ettinger, Lind, Newman, & Gardin, 1994; Reed et al., 1994; Small, Rosnick, Fratiglioni, & Bäckman, 2004; Verghese et al., 2013; Podewils et al., 2005). Given this relation to broad measures of functional status and independence, it has been suggested that carrying the e4 allele should be related to poorer performance in instrumental activities of daily living more specifically. Instrumental activities of

daily living (IADL) are skills secondary to basic survival requirements that play a major role in an older adult's ability to live independently and maintain social integration (Newsom & Schluz, 1996). IADLs include skills related to communication, driving, financial skills, shopping, meal preparation, and telephone use (Lawton, and Brody, 1969). These instrumental activities of daily living have been shown to be sensitive to changes in cognition and overall health, particularly in older adults (Schmitter-Edgecomb, Parsey, & Cook, 2011). IADLs compared to other measures of functional independence have been shown to be more sensitive to changes given findings that suggest individuals become IADL impaired before they experience impairments in their physical health and basic activities of daily living (Blazer, Fillenbaum, & Burchett 2001; Judge, Schechtman, Cress, & Group, 1996; Puente, Terry, Faraco, Brown, & Miller, 2014). However, the evidence for the relation between the e4 allele and instrumental activities of daily living in healthy older adults is mixed and not well studied. Albert and colleagues (1995) found that individuals with one or both e4 alleles reported more impairment on measures of functional independence, which included collateral reported performance on measures of IADLs, than non-carriers of the allele. Mather and colleagues (2011) found a significant relation between APOE e4 and an informant based measure of IADLs (Mather et al., 2011). However, Kulminski and colleagues (2008) found no statistically significant increased risk for self-reported disability in IADLs in carriers of either one or both e4 alleles. Blazer and colleagues (2001) found no main effect of e4 status on self-report decline in IADLs. However, women with the e4 allele had an increased risk of decline in self-report IADLs. They also found that e4 status was predictive of the development of self-reported IADL disabilities in those not previously disabled (Blazer et al., 2001). A consistent criticism of the mentioned studies examining the relation between e4 and IADLs is their reliance on self or collateral report measures and lack of measuring IADLs more

objectively. Melzer and colleagues (2005) suggest that the e4 allele is strongly associated with poorer mobility functioning (i.e., gait speed and chair stand performance) when measured by performance, but not self-reported measures of functional mobility limitations (Melzer et al., 2005). These findings provide support for the importance of further investigating differences in IADLs based upon e4 status. More specifically, support for the investigation of e4 differences in instrumental activities of daily living as measured by performance rather than self or collateral report is needed. Understanding these relations can provide the basis for determining mechanisms by which e4 may influence functional independence and subsequently may help to inform the creation of interventions that can ameliorate the likelihood of developing functional problems in older adults.

APOE e4 and White Matter

APOE plays a major role in the healthy functioning of the brain. APOE is the major lipids distributor in the central nervous system and is important in the promotion (e.g., formation of synapses) and protection (e.g., repair of acute CNS trauma) of neurons, as APOE is secreted by astrocytes and provides delivery of important lipids essential for neuronal health (Liu et al., 2013; Mahley, Weisgraber, & Huang, 2006). A method utilized to examine white matter microstructure of the brain is diffusion tensor imaging (DTI). DTI measures the movement of water molecules amongst the axons of the brain to determine the microstructure of the white matter tracts. Diffusion-weighted images are collected across time and within multiple orientations to determine the directionality and magnitude of water movement within different regions of the brain. These measurements are then paired with a mathematical model (e.g., diffusion tensor model) to describe the diffusion within each voxel and are fit to a tensor, an ellipsoid that is characterized by its three eigenvectors (v1, v2, v3) and their associated

eigenvalues (λ_1, λ_2 , and λ_3; Figure 1; Madden & Parks, 2016). Eigenvectors provide information about the orientation of the tensor whereas eigenvalues describe the strength of diffusion along the associated axes and can be combined to calculate different metrics of anisotropy and diffusion (Madden & Parks, 2016; Melhem et al., 2002; Rajagopalan Jiang, Stojanovic-Radic, Yue, & Pioro, 2017). λ_1 represents the rate of diffusion along or parallel to the orientation of the fibers while λ_2 and λ_3 provide information about the rate of diffusion perpendicular to the axonal fibers (Mukherjee, Berman, Chung, Hess, & Henry, 2008).

Within healthy white matter tracts, water molecules primarily move in an anisotropic manner, meaning that water flows in one direction parallel to the white matter fiber tracts. Abnormally high levels of isotropic movement (i.e., water molecules moving diffusely in all directions) is considered a possible indication of degradation of the white matter tract (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010). DTI utilizes four main metrics comprised of λ_1, λ_2 , and λ_3 to characterize anisotropy and diffusion (Figure 1). Fractional anisotropy (FA), is a standard summary measure of white matter microstructure and is calculated using the equation √1/2 * [√ $(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2$/ √2$(\lambda_1^2+\lambda_2^2+\lambda_3^2)$]. FA measures the diffusivity of water along the primary axis (v1) running parallel to the tract in relation to the other two axes (v2 and v3) running perpendicular to the tract and has been shown to be sensitive to microstructural changes (Alexander, Lee, Lazar, & Field, 2007; Madden & Parks, 2016). FA ranges from 0 to 1, where higher FA values represent greater anisotropy within a region (Chanraud et al., 2010). Mean diffusivity (MD) is another standard summary measure calculated using the equation $(\lambda_1+\lambda_2+\lambda_3)/3$ and represents the average magnitude of diffusion across all three axes within a voxel (Mukherjee et al., 2008). Higher MD is generally representative of greater diffusivity and

isotropy and has been shown to increase overtime in brain regions most impacted by aging in healthy older adults (Mukherjee et al., 2008; Rieckmann et al., 2016).

FA and MD are considered sensitive summary measures of pathology. Radial diffusivity (RD) and axial diffusivity (AD) are other DTI metrics thought to provide directionally specific information which can be useful in determining myelin or axonal microstructure and in detecting white matter reductions in anisotropy which can be caused by several factors such as reduced parallel diffusivity and/or increased perpendicular diffusivity (Alexander et al., 2007, Bartzokis et al., 2012; Madden & Parks, 2016). RD reflects diffusivity along the secondary axes (λ_2 and λ_3) and is thought to indicate aspects of myelin microstructure, with radial diffusivity increasing with demyelination/dysmyelination and decreasing with myelination (Suzuki, Matsuzawa, Kwee & Nakada, 2003; Rieckmann et al., 2016). Axial diffusivity (AD) reflects diffusivity along the longitudinal or primary axis, represents axonal microstructure, and has been found to significantly increase in certain brain regions overtime due to aging (Alexander et al., 2007; Chanraud et al., 2010; Rieckmann, 2016). These metrics are measured on a normalized scale and range from 0 to 1.

Research has suggested that carriers of the e4 allele exhibit decreased FA, particularly in the corpus callosum and medial temporal lobes (Persson et al., 2006). A study by Ryan and colleagues (2011) found differences in the white matter microstructure of the frontal white matter, lateral parietal white matter, the genu and splenium of the corpus callosum, and temporal stem white matter in e4 carriers as compared to non-carriers (Ryan et al., 2011). The e4 allele may be related to microstructural changes in the brain's white matter through neuronal toxicity and brain atrophy (Honea, Vidoni, Harsha, & Burns, 2009) and has been thought to also

influence white matter microstructure through neural repair, oxidative stress, and by negatively affecting myelin-producing oligodendroglia (Ryan et al., 2011).

Compared to non-carriers of the e4 allele, reductions in fractional anisotropy in the parahippocampal white matter have been reported in e4 carriers (Nierenberg et al., 2005; Tsao et al., 2014). Decreased FA in the splenium of the corpus callosum, anterior frontal lobe white matter, inferior temporal lobe white matter, and the cingulum have also been observed (Persson et al., 2006). Heise and colleagues (2011) found older adults with the e4 allele exhibited greater MD relative to non-carriers in the corona radiata, corpus callosum, superior longitudinal fasciculus, and other regions (e.g., cingulum, internal and external capsule) using whole-brain analysis with tract-based spatial statistics (TBSS; Heise, Filippini, Ebmeier, & Mackay, 2011). The e4 allele has been found to have an additive effect on normal age related changes in white matter microstructure, as evidenced by higher MD and RD in the right hemisphere along the superior longitudinal fasciculus, inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus relative to healthy middle-aged non-carriers (Operto et al., 2018). Currently there is no consensus in the directional relation between axial diffusivity and normal aging, with studies finding higher AD values (e.g., Bennet, Madden, Vaidya, Howard, D., & Howard, J., 2010; Kumar et al., 2013; Operto et al., 2018) and others finding lower AD values (Bennett et al., 2010) representing negative changes in the aging brain.

Operto and colleagues (2019) found that individuals with the e4 allele had increased vulnerability, as measured by an indirect descriptor of myelin content, in the corpus callosum, corona radiata, superior longitudinal fasciculus, and other white matter tracts when compared to non-carriers (Operto et al., 2019). These regions (i.e., corpus callosum, superior longitudinal fasciculus, and corona radiata) have connections to the frontal lobe and play a role in cognitive

processes such as executive functions and processing speed (Teipel et al., 2010; Bendlin et al., 2010; Birdsill et al., 2014). Reductions in the microstructure of white matter in these areas are consistent with those reported in individuals with mild cognitive impairment, Alzheimer's disease, and other dementias (Kantarci et al., 2001; Kantarci et al., 2005; Huang et al., 2007). Mayo and colleagues' (2018) study found that individuals with AlzD had significantly lower FA and higher MD, RD, and AD in the corpus callosum, corona radiata, and superior longitudinal fasciculus relative to healthy older adult controls (Mayo et al., 2018). Cavedo and colleagues (2017) found that cognitively intact e4 positive individuals had greater MD in the corona radiata, corpus callosum, and superior longitudinal fasciculus (Cavedo et al., 2017). This may suggest that carriers of the e4 allele may be experiencing preclinical pathological changes associated with neurodegenerative disorders and thus white matter microstructure, as measured by DTI metrics, may be sensitive early biomarkers of neurodegenerative processes.

White Matter Microstructure and Functional Independence

Degradation of white matter structures have been shown to be related to deficits in functional ability in diseases such as multiple sclerosis (MS), AlzD, and dementias more broadly (Llufriu et al., 2012; Moon, 2011; Pohjasvaara et al., 2007). Healthy older adults' ability to maintain activities of daily living have been correlated with white matter microstructure (Rosano et al., 2005). Individuals with greater deep white matter hyperintensities have shown greater deficits in their basic activities of daily living (BADLs; Park et al., 2011). A study by Gouw (2006) found that proxies for functional ability such as gait and balance were also related to deficits in white matter hyperintensities (Gouw et al., 2006). In comparison to older adults with normal brain health, those with increased white matter lesions required more help in their activities of daily living (Baune, B.T., Schmidt, W. P., Roesler, A., Berger, K., 2009). Brickman

and colleagues (2014) found a relation between positive e4 status and greater white matter hyperintensities, suggesting the impact of e4 on functional ability may be through its impact on white matter microstructure (Brickman et al., 2014).

In addition to its relation with baseline functional independence, white matter microstructure has also been related to rate of functional decline in older adults. A study by Inzitari and colleagues (2009) found that age related white matter changes (ARWMC) in older adults predicted global functioning three years later, with those with greater ARWMC experiencing greater declines in their functional abilities. Another study by Inzitari (2007) found that older adults who were functionally dependent and had severe ARWMC were at a greater risk for rapid declines in functional independence (Inzitari et al., 2007). Research by Steffens and colleagues identified that subcortical white matter lesions were associated with reductions in IADLs specifically, even after controlling for age, medical comorbidity, depression severity, and gender (Steffens, Bosworth, Provenzale, & MacFall, 2002).

Research suggests that the ability to perform these everyday activities and maintain functional independence are sensitive to changes in brain health in older adults (Schmitter-Edgecomb, Parsey, & Cook, 2011). The expected growth in the older adult population brings forth new challenges related to understanding factors that influence brain health and thus affects an older adult's ability to remain functionally independent. Due to e4's likely influence on microstructural white matter, especially in the frontal and temporal regions of the brain which are important for higher order tasks, white matter microstructure may play an important role in understanding the relation between the e4 allele and functional independence (Alvarez & Emory, 2006; Scott & Schoenberg, 2011).

Current Study

The purpose of this study was to determine the relations amongst e4, functional independence (FI) as measured by performance-based IADLs given that this is a more objective measure than self or collateral report, and white matter microstructure, more specifically, white matter microstructure of tracts that have been known to be impacted by the e4 allele (i.e., corona radiata, corpus callosum, and superior longitudinal fasciculus; Cavedo et al., 2017; Operto et al., 2018; Operto et al., 2019; Kljajevic et al., 2014; Heise et al., 2011). We predicted that e4 status would be negatively associated with performance-based IADL and white matter microstructure in a sample of community-dwelling older adults. We hypothesized that white matter microstructure and observed IADL performance would be related. Preserved white matter microstructure was measured as higher FA (Chanraud et al., 2010; Rieckman, 2016). We further examined whether there were differences in IADLs and white matter microstructure based upon e4 status. We hypothesized that individuals with the e4 allele would exhibit worse performance on IADLs and have poorer white matter microstructure.

Exploratory analyses were conducted to examine white matter microstructural differences by APOE status in specific regions of interest (i.e., anterior, superior, and posterior corona radiata and genu, body, and splenium of the corpus callosum) given heterogeneity of white matter microstructure within a tract and differences in diffusivity when white matter microstructure is examined globally versus specifically in older adults (de Groot, 2015). Other metrics suggestive of preserved white matter microstructure, as determined by lower MD and lower RD were examined. Given inconsistencies in the literature regarding the age-related changes in AD, directional hypotheses were not made for this DTI metric (Chanraud et al., 2010; Rieckman, 2016).

CHAPTER 2

METHODS

Participants

Participants for the current study were from an archival aging dataset collected within the Neuropsychology and Memory Assessment Lab at the University of Georgia. Participants consisted of community-dwelling adults, 65 years and older from the broader Athens-Clarke County area. Participants were ineligible if they had a major neurological disorder, major psychiatric disorder, were left handed, non-Native English speakers, or were not compatible with an MRI environment. There was an overall sample of 56 community dwelling older adults, with a subsample of 49 older adults who had imaging data available.

Materials

APOE e4. Blood samples were previously taken from each participant after their MRI scanning by a trained graduate student or a certified phlebotomist. The blood data was collected using Whatman FTA elute cards (Whatman Inc., Florham Park, NJ). DNA was extracted from the blood samples and analyzed by the Georgia Genomic Facility (GGF) to determine the presence of APOE alleles. DNA extraction was done following the standard protocol outlined by Whatman. Briefly, the dried elute card samples were placed in sterile microcentrifuge tubes and vortexed, water was removed and the samples were centrifuged and then heated to 95 degrees Celsius. The sample was pulse vortexed, centrifuged to separate the matrix from the eluate (which contained the DNA), and PCR was ran to isolate the target gene (APOE) and identify the

allele composition. Participants were grouped by the presence (e4 positive) or absence (e4 negative) of the e4 allele. Of the total 56 participants, 25 were e4 positive.

Functional Independence. Given the greater evidence for the efficacy of measuring performance-based IADLs, the Direct Assessment of Functional Status Revised (DAFS-R) was used as the measure of functional independence in our sample. The DAFS-R is a performance-based measure that assesses activities of daily living and can be subdivided into two domains (basic and instrumental activities of daily living). For the purposes of this study, we were interested solely in IADLs, therefore, we utilized criteria specified by Mitchell and Miller (2008) to separate the domains. The DAFS–R IADL raw scores are made up of participants' responses on tasks related to communication abilities, financial skills, shopping, transportation knowledge, meal preparation, and taking a phone message. Scores from the individual scales combine to create a total score ranging from 0–80. This measure has high test-retest reliability and interrater reliability and is a sensitive measure of functional decline in older adults (Loewenstein et al., 1989; McDougall, Becker, Vaughan, Acee, & Delville, 2009).

Diffusion Tensor Imaging (DTI). The participants underwent neuroimaging scans using a General Electric Signa HDx 3T MRI (GE). A high-resolution 3D T_1-weighted fast spoiled gradient recalled (FSPGR) sequence was utilized to collect the 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). These structural images allowed for coverage from the most superior part of the head to the most inferior part of the brain (i.e., brainstem), with a total acquisition time of no more than 7 minutes. Diffusion weighted scans were acquired using a single-shot diffusion weighted spin-echo sequence (SE-EPI). Parameters for the scan were as follows: 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 three b0 images. Two pairs of magnitude and phase images also were acquired for fieldmap-based unwarping of DW images; TE_1 = 5.0 ms and TE_2 = 7.2ms, TR = 700 ms, 60 slices, slice gap = 0 mm, 2mm 61 isotropic voxels, acquisition matrix = 128 x 128, and FOV = 256 x 256 mm. Acquisition for each pair of images took 1 minute and 40 seconds. The total DTI scan time for participants were no more than 10 minutes, although participants were involved in other scanning procedures pertaining to the larger studies.

Image Processing. T_1-weighted 3D structural images were preprocessed and segmented utilizing FreeSurfer (v5.3), an automated software program accessible online (http://surfer.nmr.mgh.harvard.edu; Fischl, 2012; Fischl et al., 2002). The FreeSurfer processing pipeline was comprised of volume- and surface-based streams that have been thoroughly detailed in previous studies (Fischl et al., 2002; Fischl et al., 2004; Gogniat, Robinson, Mewborn, Jean, & Miller, 2018). Briefly, DWI images were pre-processed using the FMRIB Diffusion Toolbox (FDT; Behrens et al., 2003) following the standard FDT 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. Brain extraction was accomplished using the brain extraction tool (BET) and distortions were corrected using the calculated fieldmaps. DTIFit (the FSL diffusion tensor imaging fitting program) was used to estimate diffusion tensors for each voxel. Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), which is a tool within FSL (Smith et. al., 2004) was used to create mean FA images. TBSS was used to determine the participant with the most representative brain scan by choosing the participant with the minimum mean displacement relative to all other participants. A mean FA image was created and thinned to make a mean FA skeleton, which signified the center of the white matter tracts that are common

to all the participants (Figure 2). Then the skeleton was created by comparing voxels in the tract perpendicular in direction and identifying the voxel with the highest FA value. A threshold FA value of 0.2 was applied to exclude voxels that may have included grey matter or cerebrospinal fluid (CSF). The mean FA diffusion values were calculated for each subject based on a priori pre-specified regions of interest (i.e., corpus callosum, corona radiata, and superior longitudinal fasciculus). These ROIs were selected given research suggesting these white matter tracts are likely impacted by e4 allele status and normal age-related changes (Heise et al., 2011; Operto et al., 2019; Rieckmann et al., 2016). The same procedural process was utilized to analyze RD, MD, and AD maps and skeletons. We overlaid the Johns Hopkins University (JHU) ICBM-DTI-81 White Matter atlas onto our voxel-wise results to determine the anatomical label of our FA, MD, RD, and AD, values that corresponded to the skeletonized maps (Mori et al., 2008).

Statistical Analysis

Primary Analyses. The Statistical Package for Social Sciences (IBM SPSS Version 21.0) was used to analyze the data. Bivariate correlations were used to analyze the relation between IADLs and mean FA of the global regions of interests. Four one-way ANOVAs were conducted with APOE status as the independent variable and IADLs, FA of the corona radiata, FA of the corpus callosum, and FA of the superior longitudinal fasciculus as the dependent variables. Benjamini-Hochberg approach with a false discovery rate of .10 was utilized to account for multiple comparisons (Benjamini & Hochberg, 1995). Age was entered in as a covariate in a one-way multivariate analysis of covariance (MANCOVA) with APOE status as the independent variable and IADLs, FA of the corona radiata, FA of the corpus callosum, and FA of the superior longitudinal fasciculus as the dependent variables.

Exploratory Analyses. A one-way MANOVA was performed to examine RD, MD, and AD differences in tracts of global white matter microstructure (i.e., corona radiata, corpus callosum, and superior longitudinal fasciculus) dependent upon APOE status. A one-way MANOVA was also used to examine the differences in FA, RD, MD, and AD in specific regions of interests (i.e., anterior, superior, and posterior corona radiata; genu, body, and splenium of the corpus callosum) dependent upon APOE status.

CHAPTER 3

RESULTS

Demographic information is provided in Table 1. Independent samples t-test and chi-square analyses revealed the two APOE status groups did not statistically differ in age, education, or gender (See Table 1).

Primary Results

Bivariate correlations revealed that IADLs were not significantly related to mean FA in the 3 global regions of interest (i.e., corona radiata, corpus callosum, superior longitudinal fasciculus), p=.457, p=.430, p=.229, respectively across the sample. When accounting for multiple comparisons using the Benjamini-Hochberg approach (Benjamini & Hochberg, 1995), there was a significant difference between performance-based IADLs dependent upon APOE status, $F(1,54) = 4.137$, p=.023, one-tailed. More specifically, e4 positive individuals performed statistically poorer on the DAFS-R than their e4 negative counterparts. There was no statistical difference between APOE groups in mean FA of the corona radiata (p=.189, one-tailed), corpus callosum (p=.112, one-tailed), and superior longitudinal fasciculus (p=.054, one-tailed). Examination of effect sizes revealed a medium effect size difference in means for performance-based IADLs (Cohen's d = .547) and small to medium effect size differences in means for FA of the corona radiata (d = .256), corpus callosum (d = .363), and superior longitudinal fasciculus (d = .486), with e4 negative older adults exhibiting greater FA. After accounting for multiple comparisons using the Benjamini-Hochberg approach (Benjamini & Hochberg, 1995) and controlling for age, the ANCOVA revealed no statistically significant differences between the

APOE groups in IADLs (p=.05, one-tailed), fractional anisotropy in the corona radiata (p=.267, one-tailed), corpus callosum (p=.223, one-tailed), or superior longitudinal fasciculus (p=.069, one-tailed).

Exploratory Results

Regarding exploratory analyses, a MANOVA was performed to examine whether there were differences in tracts of global white matter microstructure (i.e., corona radiata, corpus callosum, and superior longitudinal fasciculus), as measured by RD, MD, and AD. There were no statistically significant differences in RD, MD, or AD based on APOE status. Exploratory MANOVA analyses examining the differences in FA, RD, MD, and AD dependent upon APOE status in specific regions of interests (i.e., anterior, superior, and posterior corona radiata; genu, body, and splenium of the corpus callosum) revealed a significant difference in RD of the anterior corona radiata (p=.047, one-tailed), MD of the anterior corona radiata (p=.046, one-tailed), MD of the superior corona radiata (p=.040, one-tailed), and MD of the splenium of the corpus callosum (p=.0435, one-tailed), with e4 positive participants exhibiting greater RD and MD.

CHAPTER 4

DISCUSSION

The purpose of the current study was to examine the differences in performance-based IADLs and white matter microstructure in individuals with and without the e4 allele. As hypothesized, there was a significant difference in performance-based IADLs, such that e4 positive individuals performed worse on the DAFS-R. Notably, this was a medium effect size (Cohen's d = .547). This finding provides support for the role of the e4 allele in impacting functional independence in older adults, and one of the first examining this using a performance-based measure of instrumental activities of daily living. While there were no significant differences in more global tracts, effect sizes suggest a small to medium negative impact of the e4 allele on FA of the corona radiata, corpus callosum, and superior longitudinal fasciculus, with the superior longitudinal fasciculus exhibiting the greatest effect size (Cohen's d = .486). Given the multiple comparisons and our sample size, it is likely that our study was underpowered to detect these small to medium effects, and therefore led to nonsignificant results. Nonetheless, these findings are relatively consistent with previous findings of differences in mean FA in these regions suggesting individuals with the e4 allele exhibit worse white matter microstructure (Persson et al., 2006; Ryan et al., 2011).

Exploratory analyses examining more specific regions of interest revealed group differences in both RD and MD in the anterior corona radiata, MD group differences in the superior corona radiata, and MD group differences in the splenium of the corpus callosum. Studies suggest the superior corona radiata plays some role in processing speed and executive

function (Birdsill et al., 2014), and white matter microstructural changes in the anterior corona radiata are related to both cognitive and executive function (Bendlin et al., 2010; Birdsill et al., 2014). These findings provide some support to the use of other metrics of white matter microstructural changes that might be more sensitive to white matter microstructural differences. Given e4 allele individuals experienced poorer performance in IADLs, which have been shown to be sensitive to changes in cognition and executive function (Schmitter-Edgecomb et al., 2011), although white matter microstructure was not correlated to IADLs, these findings could be indicative of these regions playing a role in functional independence. Furthermore, given differences in white matter microstructure were found when examining more specific regions of interests rather than when combined in more global regions, this study provided evidence for examination of specific white matter microstructures rather than more global regions.

This study is not without limitations. The greatest limitation is one of power. The current study was powered to find medium effect sizes (Cohen's d = .381) not accounting for multiple comparisons. When accounting for several comparisons, the power of the study reduced and thus limited our ability to determine small or medium group differences in white matter microstructural changes in older adults. Another limitation of this study is the homogeneity of this current sample. Individuals in this study were relatively highly educated and majority Caucasian therefore limiting the generalizability of this study. The homogeneity of the sample may have also played a role in the limited findings of differences in white matter microstructure dependent upon APOE status. For instances, several environmental factors such as education, job complexity, and income have been related to worse cognitive and brain health outcomes (Meng & D'arcy, 2015; Snyder et al., 2015) along with studies that provide evidence for racial differences, which are likely linked to environmental and socioeconomical disparities, in brain

health in older adults (Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Cagney, Browning, & Wen, 2005). Thus, examining the current study in a more heterogeneous sample may provide more generalizable information about the relations between APOE status, IADLs, and white matter microstructure.

Nonetheless, this study utilized a performance-based measure to assess instrumental activities of daily living, a proxy measure for functional independence, which is generally shown to be a better measure of functional independence in older adulthood than more subjective measures, such as self-report or collateral report of IADL performance (Mitchell & Miller, 2008; Schmitter-Edgecombe, Parsey, & Cook, 2011). Additionally, this study examined both common (FA) and less common (RD, AD) measures of white matter microstructure. The current study identified that individuals with the e4 allele have significantly worse performance in instrumental activities of daily living. Although IADL performance was not related to measures of white matter microstructural changes, exploratory analyses provided insight into possible use of other metrics to assess white matter microstructure differences that may be more sensitive to differences based on genetic risk level.

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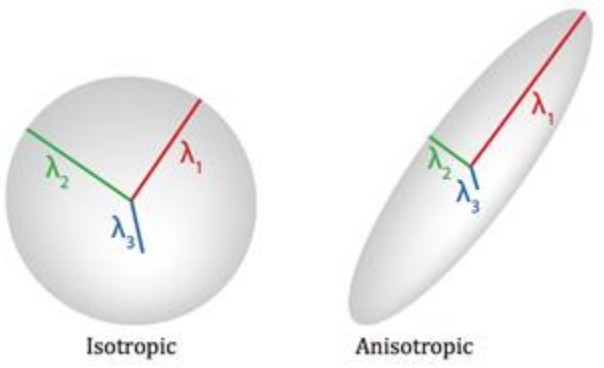

Figure 1. Visual schematic of a diffusion tensor and measures used to determine anisotropy and diffusion.

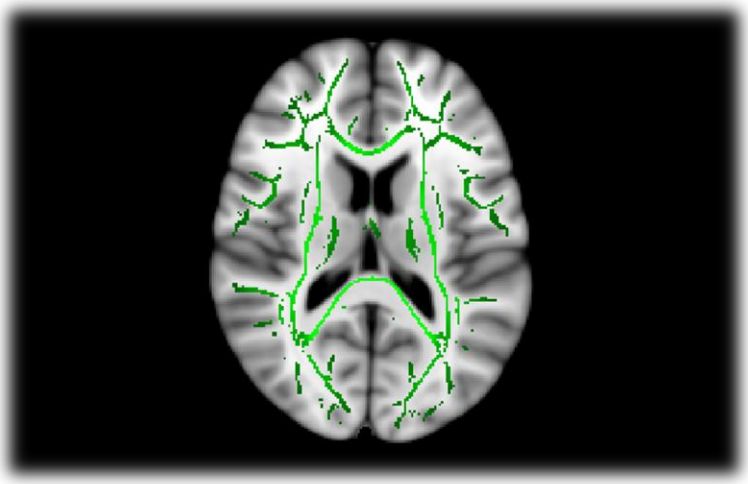

Figure 2. An illustration of the mean FA skeleton mask highlighted in green (.2 - .7 threshold) overlaid onto the MNI152 brain template. The image is shown in the axial view and was viewed and taken from FSLview.

Table 1. Demographic Information and Differences by APOE status

	e4 positive (n = 21) M (SD)	e4 negative (n=26) M (SD)	p-value	Total Sample (n=47) M (SD)
Age	76.2 (5.58)	73.1 (5.85)	.051	74.55 (5.7)
Education	15.48 (3.02)	16.09 (2.36)	.394	15.89 (2.45)
Race	96% Caucasian	93% Caucasian	.194	95.7% Caucasian
Gender	60% female	64% female	.252	66% female

Note. M = mean; SD = standard deviation.