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Introduction

As life expectancy and the number of older adults continues to rise every year, it becomes imperative to understand the underlying mechanisms behind the development of dementia. Dementia is a broad term for a group of disorders categorized by severe cognitive decline and functional changes that lead to altered performance in day-to-day activities (Alzheimer's Association, 2021; Barnes et al., 2012). The dementia related costs for care in the United States (U.S.) were over $290 billion in 2019 and are expected to increase to more than $1.1 trillion in 2050 (Alzheimer's Association, 2019). The most usual form of dementia is Alzheimer's Dementia, a progressive and unremitting neurodegenerative disease making up between 60-80% of all dementia cases. As of now, no effective treatment has been developed to prevent or cure Alzheimer's Dementia, and it is predicted that the number of individuals affected with this illness will rise from the current 5.8 million Americans to as high as 13.8 million by the year 2050 (Alzheimer's Association 2019). Alzheimer's Disease (AD) itself refers to the entire disease process, which is defined as a cognitive continuum marked by a preclinical state, a prodromal state, and ultimately a dementia state (Jack et al., 2011; McKhann et al., 1984; McKhann et al., 2011). Thus, Alzheimer's dementia specifically refers to clinically diagnosed dementia characterized by established criterion and as a result of probable AD brain pathology (Alzheimer's Association, 2021; McKhann et al., 2011). This pathology is characterized by clusters of amyloid-beta (Aβ) peptides, known as amyloid plaques that are found in excess extracellularly and with intracellular aggregations of tau protein called neurofibrillary tangles (NFTs) (Braak & Braak, 1991; Jack et al., 2018; McKhann et al., 2011).

On neuroimaging, early neuropathological manifestations of AD are often noted in the medial temporal lobe and the limbic region, particularly the hippocampus and parahippocampal gyrus; which are structures connected to the cognitive domains of memory and semantic fluency (Risacher et al., 2009; Stark & Stark, 2017; Wang et al., 2015). These regions also experience atrophy, which is the AD biomarker that is most closely associated with cognitive outcomes (Jack et al., 2018). Accordingly, the most commonly used neuroimaging biomarkers rely on volumetric measures from structural magnetic resonance imaging (MRI), and the recent implementation of machine learning practices has begun to drastically increase the accuracy of this method in identifying AD-related atrophic change (Casanova et al., 2020; Kumar et al., 2021; Vemuri & Jack, 2010; Wang et al., 2015). One such technique is the Spatial Pattern of Abnormality for Recognition of Early Alzheimer's disease (SPARE-AD). This measure can discern patterns of brain atrophy across the cognitive continuum at a higher level of accuracy than simple volumetric measurements of regions of interest (Fan et al., 2008). Importantly, this technique shows promising predictive utility among preclinical samples (Davatzikos et al., 2011). An increased focus on preclinical samples is critically needed given the paucity of studies within this state of the AD cognitive continuum, and its relevance in primary prevention. Further, much is still unknown regarding the degree to which brain atrophy mediates the cognitive correlates associated with genetic AD risk in the preclinical phase.

The neuroanatomic and cognitive consequences that so well define the AD-pathophysiological process have been linked to the genetic risk profile of individuals (Braak & Braak, 1991; Jack et al., 2018; Masters et al., 2015; Tanzi, 2012). Famously,

the Apolipoprotein E (APOE) gene has been extensively studied and tied to AD due to its role in breaking down Aβ before it can form plaques, with a particularly ineffective variant (APOE ε4) associated with an increased risk for AD (Elahi & Miller, 2017; Mahley, 1988; Masters et al., 2015; Sheppard & Coleman, 2020; Tanzi, 2012). In terms of the relationship between the APOE ε4 allele and cognition, the presence of even a single allele has been observed to confer a high risk of progression across the cognitive continuum, including conversion from normal cognition to mild cognitive impairment (MCI) and from MCI to AD (Boyle et al., 2010; Elias-Sonnenschein et al., 2011; Ren et al., 2020; Risacher, 2013; Varatharajah et al., 2019). However, although one prior study has used APOE risk status to improve the predictive utility of the SPARE-AD index (Da et al., 2014), none have examined if AD-specific neurodegeneration - indexed by SPARE-AD -partially explains the relationship between genetic risk and AD-specific cognitive performance.

Although APOE ε4 clearly relates to cognitive decline and neurodegeneration in a rising aged population, the magnitude of risk conferred by the ε4 allele varies by population, particularly with African American samples demonstrating a weaker association (Fillenbaum et al., 2001; Maestre et al., 1995; Mayeux et al., 1993; Rajabli et al., 2018; Ren et al., 2021; Sawyer et al., 2009; Tang et al., 1996; Weuve et al., 2018). Although African Americans have double the risk for incident AD and a higher frequency of the ε4 allele compared to individuals of other races/ethnicities, due to methodological limitations of previous studies and potential racial differences in AD-pathophysiological mechanisms, the literature remains mixed regarding ε4's impact on cognitive and neuroanatomical profiles in African Americans (Alzheimer's Association,

2021; Maestre et al., 1995; O'Donoghue et al., 2018; Weuve et al., 2018). In relation to APOE ε4-brain correlates along pertinent structures, like the temporal lobe and hippocampus, there is some evidence that the associations of atrophy and cognition may be moderated by race wherein the impact of volumetric changes on cognitive performance are steeper for African American cohorts than their White counterparts (Howell et al., 2017; Gu et al., 2015;). Even in instances of comparable brain changes, it has been documented that African Americans may experience more stark cognitive decline than Whites (Howell et al., 2017). As a whole, a clear pattern regarding ε4-cognition and ε4-brain associations among African Americans has yet to emerge, with some evidence pointing towards potential racial differences in the deleterious effects of ε4, but continued methodological limitations likely contributing to the inconsistencies within the literature (O'Donoghue et al., 2018; Sawyer et al., 2009). These potential racial differences in ε4-brain and cognition correlates have not been explored with SPARE-AD which offers an opportunity to add a novel perspective to the literature pertaining to the ε4 allele's influence on neurodegenerative profiles, and ε4–related cognitive performance, in a diverse sample.

Taken together, it appears that APOE ε4 carrier status imparts a negative effect on AD-specific cognitive decline; however, whether and how it impacts measures of cognitive performance via neurodegeneration has yet to be fully explored. Additionally, among African Americans the association between ε4 carriership and brain-cognition correlates still requires further examination with more rigorous methodologies and adequately sensitive measures to assess if there are true racial differences in preclinical samples. The purpose of the proposed study was to examine whether the association of

the APOE ε4 allele and performance on cognitive tests that are associated with patterns of AD risk (i.e., memory, semantic fluency) are moderated by race and mediated by the SPARE-AD index while adjusting for sex, poverty status, literacy, and age in a sample of socioeconomically diverse urban-dwelling adults.

This document first provides a definition of AD and its diagnostic frameworks. This is followed by an overview of AD-specific brain and cognitive correlates. Then, definitions of the prodromal and preclinical states of AD are provided. Next is a discussion of the genetic underpinnings of AD, with a particular focus on APOE ε4. Subsequently, an overview of APOE and its relation to brain and cognitive outcomes in preclinical samples is provided. This is followed by an examination of race and its association with APOE ε4's AD-related outcomes, and a rationale for the current covariates of the study. Finally, a statement of the problem, the study aims, hypotheses, methodology, and data analytic procedures are outlined.

Literature Review

Alzheimer's Dementia

Alzheimer's Disease dementia is a chronic, unremitting, and irreversible neurodegenerative disease marked by functional impairments and cognitive impairment in the domains of memory, language, executive functions, and/or visuospatial abilities (Masters et al., 2015; Sheppard & Coleman, 2020). The average survival of aging adults with AD dementia ranges from four to ten years, with some individuals far exceeding this range (Alzheimer's Association, 2019; Masters et al., 2015; Tom et al., 2015). The original guidelines for the diagnosis of probable AD dementia was recommended by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)

and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup in 1984, where it was believed that it had only one stage - the dementia stage (Jack et al., 2011; McKhann et al., 1984; McKhann et al., 2011). During this time, diagnosing AD with absolute certainty was done solely by examining neural tissue postmortem for amyloid plaques and neurofibrillary tangles. Amyloid plaques (Aβ) are clusters of Aβ-peptides found in excess extracellularly, while neurofibrillary tangles (NFTs) are intracellular accumulations of tau protein. Both are hallmark biomarkers in defining AD neuropathology and are implicated in neuronal dysfunction and dementia progression (Jack et al., 2018; McKhann et al., 2011). An antemortem diagnosis was typically based on criteria outlined from observed clinical symptomology and performance on neuropsychological tests. After nearly three decades of research on the topic, the diagnostic guidelines were revised by the National Institute on Aging (NIA) and the Alzheimer Association (AA) workgroups as it became apparent that there are instead three distinct entities: preclinical, prodromal, and Alzheimer's dementia phases that are characterized by specific biomarkers that impact and reflect disease progression (Jack et al., 2011; McKhann et al., 2011). These guidelines were recently revised again, shifting from three distinct clinical entities to a cognitive continuum model with preclinical, prodromal, and dementia profiles running along the spectrum (Jack et al., 2018). The term Alzheimer's Dementia specifically refers to the end of the cognitive continuum and entails a diagnosis of dementia that is likely caused by the AD pathophysiological process and determined through specific criteria and guidelines (Alzheimer's Association, 2021; Jack et al., 2018; McKhann et al., 2011).

The clinical diagnosis of probable AD dementia is characterized by eight criteria: 1.) It interferes with the ability to function socially or occupationally; 2.) Represents a decline from prior levels of performance and functioning; 2) Cannot be explained by delirium or a major psychiatric disorder; 3.) Cognitive impairment as diagnosed through interviewing the patient and a knowledgeable informant and through an objective cognitive assessment such as a neuropsychological battery or mental status assessment; 4.) Impairment in two or more of the following areas- ability to acquire and remember new information, executive function, visuospatial abilities, language function, and changes in behavior; 5.) Insidious onset; 6.) Unambiguous history of cognitive decline from self-report or observation; 7.) Predominantly demonstrating cognitive deficits that are either an amnestic pattern or non-amnestic but within the domains of word-finding, visuospatial, or executive function; and finally, 8.) If there is no presence of a concurrent dementia (e.g., frontotemporal dementia, Dementia with Lewy bodies, etc.), cerebrovascular disease, or other comorbidity that significantly impacts cognition (McKhann et al., 2011).

Additionally, if this last criteria is not met, then the diagnosis would fall under possible AD due to a mixed etiological presentation (McKhann et al., 2011). Although dementia subtypes differ greatly in their symptomology, etiology, and pathophysiology, there are many cases of individuals with more than one dementia pathology, known as mixed dementia (McKhann et al., 2011; Rahimi & Kovacs, 2014). In a review of 12 community-based studies investigating mixed dementia prevalence, it was found that the frequency of possible AD due to a mixed etiological presentation ranged from 28%-74% (Rahimi & Kovacs, 2014). Additionally, this review found that the most prevalent form

of mixed dementia was that of co-occurring AD and vascular dementia (VaD) (Rahimi & Kovacs, 2014). A limitation of this review (and the studies analyzed therein) is that methodologically, the studies reviewed primarily relied on neurofibrillary degeneration to assess AD-pathology postmortem. Although the level of neurofibrillary degeneration often aligns well with clinical dementia status, AD pathology can often precede cognitive impairments, which still leaves the possibility that some participants that met the neuropathological criteria may not have been in the dementia phase of the AD continuum, since the clinical diagnostic guidelines were not prioritized (Hampel et al., 2008; Hyman et al., 2012). It is additionally noted in the review that there is an overlap of etiological factors between typical AD neuroanatomical changes and those of vascular dementia involving instigation by cardiovascular disease (CVD) risk factors. Further refining biomarkers to distinguish among dementia subtypes would ultimately help in generating AD-specific neuroimaging tools and methodologies.

Typically, CVD risk factors are most closely associated with VaD, which is a form of dementia that most prominently impacts executive function, is attributable to cerebrovascular pathologies, and is the second most common form of dementia after AD dementia; however, these risk factors overlap with AD neuropathology as well (Gorelick et al 2011; Iadecola, 2013; Wolters & Ikram, 2019). In an extensive review of the literature pertaining to the pathobiology of vascular dementia, it is delineated that several mechanisms overlap with AD neuropathology (Iadecola, 2013). For one, prolonged exposure to CVD risk factors (e.g., hypertension, atherosclerosis, hyperlipidemia, and diabetes) contributes to vascular damage, and disrupts various functions of the cerebral blood vessels (Iadecola, 2013). This results in pathophysiological consequences that

appear in both VaD and AD, such as: endothelial dysfunction, altered immune trafficking, impaired delivery of oxygen to the brain, and an increased propensity for vascular lesions. The synergistic and cumulative impact of these cardiovascular insults leads to reduced cerebral perfusion, infarcts, small vessel disease, cerebral amyloid angiopathy (CAA), and other lesions that not only present in VaD but also co-occur in nearly 50% of AD cases (Iadecola, 2013; Jellinger, 2013; Love & Miners, 2016; Rahimi & Kovacs, 2014; Stampfer, 2006). Despite some of these overlaps in neuropathology, there are distinct neuroanatomical correlates that differentiate VaD and AD (Elahi & Miller, 2017; Fan et al., 2008; Fox et al., 1996; Schuff et al., 2008; Sheppard & Coleman, 2020). It is no surprise then, that the certainty of clinical diagnosis for probable AD can be further bolstered by evidence from select neuroimaging measures specific to AD pathophysiology (Jack et al., 2018; McKhann et al., 2011; Vemuri et al., 2011; Vemuri & Jack, 2010; Wang et al., 2015). Accordingly, although overall AD may have neuropathological overlap with VaD, distinct neuroanatomical, cognitive, and clinical criteria exist to ensure that AD is accurately being studied. These distinct measures are pivotal for properly understanding the brain-correlates specific to AD-pathophysiology.

AD-Specific Brain Correlates

The first recorded case of AD was in 1906, when the histological examination of the brain of a postmortem patient—previously experiencing extensive memory loss, progressive confusion, and sleep disturbance—revealed the presence of amyloid plaques, NFTs, and severe atrophy throughout the cerebral cortex (Cipriani et al., 2011; Graeber et al., 1998). Over the years, further histological approaches localized specific brain regions most often affected by AD neuropathology, specifically the superior temporal gyrus,

inferior parietal lobe, mid-frontal cortex, occasionally the occipital cortex (including primary visual cortex and association cortex), and the hippocampal formation (Hyman et al., 2012; Hyman & Trojanowski, 1997; Khachaturian, 1985). These approaches further elucidated that AD neuropathology could be present even in the absence of an observed or diagnosed dementia (Hyman et al., 2012; Hyman & Trojanowski, 1997; Jack et al., 2018; Sperling et al., 2011).

The histological approach is the most definitive imaging method of diagnosing AD; however, it cannot be done non-invasively and is typically a postmortem strategy (Hyman et al., 2012; Hyman & Trojanowski, 1997; Jack et al., 2018; Sperling et al., 2011). Thus, this approach leaves little possibility to use clinically (other than retrospectively) or to track changes (either neuroanatomically or cognitively) in living individuals. Advances within in vivo neuroimaging and biomarker analysis have resulted in viable proxies to measuring AD-specific neuropathological changes, which has been detailed by the NIA-AA research framework (Jack et al., 2018). This framework builds upon the revised diagnostic guidelines from the NIA-AA workgroups in 2011 to showcase recent findings in AD neuroimaging biomarker associations and provides applicable guidelines towards utilizing AD biomarkers in research (Jack et al., 2018). A tripartite classification system has been developed to track biomarkers based on Aβ deposition, pathologic tau aggregation, and neurodegeneration (abbreviated as ATN profiles); which is flexible enough for the introduction of new biomarkers to fall within these three categories as the literature continues to expand (Jack et al., 2018). This framework and a growing body of literature suggests that there is a possibility for reliably observing substantial neuroanatomical changes in those with probable or possible AD

antemortem. This notion utilizes and evolves neuroimaging biomarkers to further understand AD-specific trajectory via brain correlates in living individuals.

The most prominent methodology to study in vivo Aβ deposition is through amyloid positron emission tomography (PET) (Chandra et al., 2019; Jack et al., 2018; Marcus et al., 2014). For this method, an individual is injected with an active radiotracer that binds to the Aβ clusters so that regions with higher binding to the compound reveal a greater concentration of Aβ deposition (Chandra et al., 2019; Marcus et al., 2014). The first and most widely studied radiotracer created for this method was ^{1}C-labelled Pittsburgh compound B ([^{11}C]PiB), which demonstrates strong affinity and selectivity to amyloid; however, its 20-minute half-life and the expensive equipment needed to synthesize the positron-emitting isotope has made it difficult to use in non-academic settings (Chandra et al., 2019). This led to the creation of three FDA approved radiotracers with longer half-lives that were more viable for clinical settings (Chandra et al., 2019).

In a recent systematic review of 15 studies on the application of PET imaging, it was revealed that the three FDA approved tracers had equivalent diagnostic accuracy and comparable diagnostic utility to [^{11}C]PiB (Chandra et al., 2019). Furthermore, amyloid PET not only displays high sensitivity and specificity to AD diagnoses, but exhibits the ability to measure Aβ deposition that is later confirmed in post-mortem brain tissue analysis (Chandra et al., 2019). The common brain regions with high radiotracer binding across the 15 reviewed studies were the cingulate (posterior and anterior), precuneus, frontal, parietal, and lateral temporal cortex; while, the pons, subcortical white matter, and the cerebellum were spared from radiotracer binding (Chandra et al., 2019). These

regional findings regarding Aβ deposition also parallel typical histological studies (Braak & Braak, 1991). That is to say that amyloid PET holds strong diagnostic utility in AD pathology given its direct measurement of Aβ deposition in vivo, which is a primary biomarker of interest proposed by the NIA-AA framework. Despite this, there are some limitations to the amyloid PET methodology that are overlooked in this systematic review. Aside from the cost of amyloid PET, the methodological complexities of developing and delivering the radiotracers within their half-life does not align easily with study protocols that require frequent follow-ups or rely on mobile/at-home research visits. Thus, studies may have little opportunity to probe various etiological risk factors of AD due to the time and cost of this biomarker. Thus, there is an overall lack of population-based studies pertaining to this methodology, which further limits its translation to diverse populations. This ultimately suggests that amyloid PET is a somewhat restrictive AD biomarker to use, and that other biomarkers may be better suited for consistent AD-brain analysis.

This same systematic review highlighted the rising literature pertaining to tau-based PET, and its emerging findings in vivo (Chandra et al., 2019). Historically, studying tau and neurofibrillary tangle biomarkers has been exceedingly difficult given the nature and localization of the biomarker. As an intracellular aggregate, measuring this biomarker was often relegated to invasive lumbar punctures to acquire cerebrospinal fluid (CSF) or was left for histological approaches post-mortem; however, advances in tau neuroimaging have made this measure slightly less limited (Chandra et al., 2019). Much like amyloid PET, tau-based approaches rely on radiotracers to bind with tau aggregations, with higher tracer accumulations being associated with a higher

concentration of tau and thus a measure of NFT presence (Chandra et al., 2019). Neuroanatomically, tau-binding is seen at higher concentrations along the medial temporal lobe (MTL), including the hippocampal formation, with progression into the neocortex (Chandra et al., 2019). From a clinical utility perspective, tau-based PET differs from amyloid PET in that the presence of NFTs has a strong association with cognitive outcomes while Aβ deposition holds a much weaker association (Chandra et al., 2019).

Despite this, much of the same limitations discussed for amyloid PET ring true for tau-based PET, although there is the added barrier that the tau PET literature is still relatively nascent in comparison to the more established amyloid measure. For example, few of the tau-specific tracers have been compared against each other in terms of diagnostic accuracy, and the literature pertaining to the second generation of tracers is only just being published (Chandra et al., 2019). The limitations of these biomarkers shift the focus away from Aβ deposition and NFTs (the A and T in the ATN profiles) to the third hallmark biomarker within the NIA-AA's AD research framework: neurodegeneration. This is a neuroimaging biomarker that achieves a high association with cognitive performance, is more readily applied to population-based studies, and correlates strongly with AD pathophysiology (Talwar et al., 2021; Vemuri & Jack, 2010; Wang et al., 2015).

Focusing on neurodegeneration patterns leads to the realm of structural MRI, a non-invasive neuroimaging biomarker that elucidates information on atrophy and volumetric abnormalities by providing a visualization of gray matter, CSF, and white matter structures (Talwar et al., 2021). Although the use of structural MRI and the

presence of neurodegeneration is not specific to AD pathology, there are strong AD-specific patterns of atrophy that make this neuroimaging technique particularly powerful (Talwar et al., 2021). In a recent systematic review of neuroimaging correlates in AD, it was found that across 13 structural MRI meta-analyses, the progression of observed total brain neurodegeneration most commonly begins within the MTL (including the hippocampal formation), progresses into the posterior cingulate cortex, followed by the lateral temporal cortex, and major aspects of the neocortex (frontal, temporal, and parietal) (Talwar et al., 2021).

Not surprisingly, these stages of neurodegeneration parallel the pathological staging of NFTs in the brain—typically progressing from the trans-entorhinal area, to the limbic regions, to all isocoritcal structures—because the development of NFTs seems to be at least partially responsible for neuronal loss and atrophy (Braak & Braak, 1991; Talwar et al., 2021). What the findings of this review ultimately suggest is that structural MRI not only directly measures atrophy of neuroanatomical structures, but indirectly measures NFT burden. This further solidifies the strength of MRI-based measures as an AD biomarker, as long as the structural analyses follow the AD-specific regions of neurodegeneration detailed above. This is an essential distinction because other forms of dementia also display distinct patterns of neurodegeneration, although they may occasionally overlap in regions with AD (as discussed previously regarding mixed dementia presentations). It is for this reason that most MRI studies focus on atrophy of the MTL and hippocampal formation, as these are the first regions to experience NFT development, Aβ deposition, and corresponding neuronal loss in AD.

One study sought to validate the notion that MRI findings of select hippocampal regions was directly associated with histologically confirmed neuronal loss, while also developing a neuroanatomical distinction between AD pathology and VaD pathology (Zarow et al., 2005). This study took brain samples from 28 cases from the Ischemic Vascular Dementia (IVD) Program Project and the Honolulu Asia Aging Study (HAAS) and confirmed the diagnosis (via histological methods) revealing a total of nine samples with AD, six with VaD, two comprising a mixed dementia, five cognitively impaired (but not matching a dementia diagnosis), and six healthy controls (Zarow et al., 2005). Premortem MRIs were conducted and compared to postmortem histological neuronal counts to determine if atrophy observed via MRI matched with observed atrophy in histological methods.

It was determined that in the cornu ammonis 1 (CA1) region of the hippocampus, MRI indeed accurately measured neuronal loss, hippocampal volume, and brain weight across dementia type (Zarow et al., 2005). In contrast, these results did not hold true for the CA2 regions of the hippocampus despite correlating with CA1 in terms of volume and neuronal number. CA1 hippocampal atrophy measured by both MRI and neuronal counting was more pronounced in the AD brain samples than the VaD patients, and in fact, VaD hippocampal CA1 neuronal numbers were comparable to those of the healthy controls (Zarow et al., 2005). Furthermore, smaller hippocampal CA1 regions were strongly associated with poorer performance on a list learning test involving delayed, cued, and immediate recall from the Memory Assessment Scales (Zarow et al., 2005). This study ultimately highlights three key points: 1.) structural MRI is an accurate biomarker for neurodegeneration 2.) when used to observe regions that are associated

with AD via established theoretical frameworks, MRI measures can distinguish between AD and other types of dementias 3.) structural MRI of AD-specific brain regions correlate with the symptomatic manifestations of AD (i.e., memory impairment). This further demonstrates the utility of structural MRI as a biomarker for AD and its potential to highlight not only AD-specific brain correlates, but AD-specific cognitive correlates as well.

Despite these findings, a major limitation of the study is actually its reliance on a specific region of interest. The fact that significant findings were only found for the hippocampal CA1 region, but not the CA2 region suggests that a dependence on hypothesis-driven neuroanatomical analysis may leave studies vulnerable to select an inappropriate brain endpoint for any given sample. This ultimately is a major drawback for most region of interest (ROI) structural MRI studies—the need for an *a priori* decision on which brain structure(s) to focus on. Focusing on only specific ROIs limits the scope of observed spatio-temporal patterns of neurodegeneration in the AD brain. One method in which this can be avoided is through whole brain voxel-based morphometry (VBM), which relies on total white matter or gray matter atrophy as a measure (Wang et al., 2015). This creates a hypothesis-free approach in MRI based research, which allows for patterns of AD-specific neurodegeneration to be assessed.

A meta-analysis of 960 AD individuals across 30 VBM studies determined that across these studies, a pattern of GM volumetric reductions were present in the limbic regions (specifically the left posterior cingulate gyrus and left parahippocampl gyrus), fusiform gyrus, and right superior frontal gyrus (Wang et al., 2015). These findings persisted even after sensitivity analyses and suggest that these structures form a linked

default mode network (DMN) in which the neurodegeneration of one region may instigate neurodegeneration in another.

A limitation of this analysis is that most of the studies analyzed were of older adults with mean education ranging from 7-16 years, leading to a wide range of potential confounding risk factors based on sample selection bias. Additionally, VBM methodologies are highly variable and may not accurately reflect in vivo AD neuropathologic changes. This is primarily due to the fact that AD progression is heterogenous across racial groups, and even the neuroanatomical endpoints affected may differ drastically between individuals, across ethnic groups, and within populations (Davatzikos et al., 2009; Rizzi et al., 2014; Wang et al., 2015; Yaffe et al., 2013). In fact, methods to differentiate AD-specific atrophy from neurodegeneration via VaD or mixed etiology were not specified in this meta-analysis, leaving the risk for mixed dementia participants to be included in this review. The ability to discern between AD-specific neurodegeneration and those of a mixed etiological presentation is paramount within the present proposal due to the evidence that African Americans are more likely to have a mixed dementia pathology compared to Whites (Barnes et al., 2015).

This is exemplified in the post-mortem evaluation of 122 brain samples from the Rush Alzheimer's Disease Clinical Core prospective study, in which participant samples (41 African Americans and 81 Whites) were matched two-to-one by age, sex, education, and mental status measured by Mini-Mental State Examination (MMSE) proximal to death (Barnes et al., 2015). This revealed that Whites were nearly twice as likely to have a single dementia pathology compared to African Americans, and that African Americans had a 20% higher likelihood of a mixed dementia pathology (Barnes et al., 2015). African

Americans also experienced a nearly 50% higher likelihood of arteriolar sclerosis and 30% higher atherosclerosis (Barnes et al., 2015). This suggests that African Americans are more vulnerable to small and large vessel disease and the risk factors that precipitate mixed dementia. What makes this autopsy study fascinating is that it addresses a major gap in the neuropathological literature—the fact that most of these studies were done in predominately White samples (Barnes et al., 2015). The paucity of neuropathological data in African Americans and the higher likelihood of mixed dementia in this population suggests that a highly specific and sensitive atrophy biomarker should be utilized to probe racial differences in AD-specific brain correlates. This emphasizes the need for a more selective, yet automated approach at studying AD-specific neurodegeneration within MRI analyses. This is where artificial intelligence (AI) and machine learning approaches have begun to shine within the space of neuroimaging.

Machine learning is a branch of AI that can take large-scale data and accurately discern patterns, generate predictions or follow decision trees, and model relationships based on outcomes and entered data to further streamline clinical diagnostic approaches (Kumar et al., 2021; Lin et al., 2021). As AI has advanced over the years, there has been growing interest in integrating this tool with neuroimaging techniques to facilitate the diagnosis and prediction of AD (Kumar et al., 2021; Lin et al., 2021). An important caveat to this methodology is that the protocols guided by machine learning models must be supervised and validated by those with an in-depth understanding of the AD literature to certify precise and appropriate outcomes (Kumar et al., 2021). This is additionally achieved by tasking machine learning protocols to use neuroimaging data for the development of data-driven algorithms that improve the predictive utility of these

biomarkers and in turn increase the diagnostic accuracy of AD (Kumar et al., 2021). In fact, MRI measures are the most widely used neuroimaging technique integrated with machine learning for the predictive modeling of AD (Kumar et al., 2021). This is likely due to the same limitations in using amyloid and tau biomarkers that are outlined above in this present review. In contrast, MRI-based measures of neurodegeneration for the prediction and diagnosis of AD-specific brain outcomes are well-suited to machine learning protocols. Furthermore, the limitations of MRI as an AD biomarker can be overcome and improved upon by the integration of these machine learning methods to ultimately expand the current literature regarding AD-specific neurodegenerative profiles.

The Emergence of SPARE-AD as Biomarker

One specific AD biomarker that integrates machine learning and MRI-based measures is the Spatial Pattern of Abnormality for Recognition of Early Alzheimer's disease (SPARE-AD) index. This index was built using T_1-weighted structural scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and supervised support vector machine learning methods to generate a high-dimensional non-linear pattern classification method (Davatzikos et al., 2009; Fan et al., 2008). This computer-based classification method relies on individual patient analysis, aiming to categorize individual scans belonging to participants with AD against those that are cognitively normal in the ADNI (Davatzikos et al., 2009; Fan et al., 2008). This approach considers all brain regions together and identifies a minimal set of regions whose volumes optimally differentiate between those with AD and those that are cognitively normal on an individual scan basis (Davatzikos et al., 2009; Fan et al., 2008). This classification

method creates an algorithm that can calculate a SPARE-AD index for an individual and can be applied to the MRI measurements of other studies (e.g., the Baltimore Longitudinal Study of Ageing (BLSA) (Davatzikos et al., 2009; Fan et al., 2008).

A more positive SPARE-AD index denotes a more AD-like pattern of atrophy while a more negative score denotes a more typical brain morphology (Davatzikos et al., 2009). Of note is that this integration of MRI measures with machine learning methodologies moves away from ROI or VBM based methodologies typically seen in MRI studies of AD for a more robust classification approach. In a leave-one-out cross-validation to test this classification algorithm on datasets not used for training, it was determined to be 94.3% accurate in distinguishing AD-like brain correlates from normal brain morphology (Fan et al., 2008). In contrast, ROI volumetry had an 82% accuracy when computed with the leave-one-out cross-validation (Fan et al., 2008). These results suggest that the SPARE-AD index is a more specific and sensitive measure for AD identification than an ROI approach. This implies that this neurodegeneration index approach ultimately compensates for the limitations of structural based MRIs discussed earlier, by producing an unbiased, automatic, and hypothesis-free measure of spatio-temporal atrophy.

SPARE-AD goes beyond simply assessing total group differences between those with AD pathology vs those without AD pathology, and further presents a specific and sensitive predictor of AD status for any given individual. This measure of neurodegeneration likely reflects a pattern of synapse loss, which is the aspect of AD neuropathologic change that most closely correlates with clinical symptoms (Jack et al., 2018). Thus, the strength and predictive power of SPARE-AD showcases its utility and

begins to justify the rationale for its use as a biomarker and mediator for the present study. What the SPARE-AD literature currently fails to address is its possible utility in accurately probing racial variability within the realm of AD-specific neuroimaging. The racial differences in atrophy patterns are evidenced by the higher likelihood of vascular pathology, small vessel disease, and mixed dementia in African American samples (Barnes et al., 2015) and exacerbated by the lack of applied machine learning protocols in neuroimaging within this population. Despite its relatively new nature, the SPARE-AD biomarker has potential to establish highly specific AD-atrophy patterns in African American samples. It further provides a pathophysiological measure for the primary phenotype of AD: cognitive impairment (Da et al., 2014; Davatzikos et al., 2009; Masters et al., 2015; Sheppard & Coleman, 2020) .

AD-Specific Brain-Cognition Correlates

Before discussing the associations between SPARE-AD and cognition in AD participants, it is important to highlight the basic associations between AD-specific brain regions and their corresponding cognitive domains. As discussed in the above section, the MTL (including the hippocampal formation), posterior cingulate cortex, lateral temporal cortex, and major aspects of the neocortex are affected by the progression of AD (Braak & Braak, 1991; Talwar et al., 2021). These regions experience gradual accumulation of Aβ and neurofibrillary tangles, which eventually results in neurodegeneration (Braak & Braak, 1991; Talwar et al., 2021). As a whole, this neurodegenerative process is exemplified by volumetric reduction of these regions (Sheppard & Coleman, 2020). This seems to occur as the progression of AD results in neuronal atrophy and synapse loss, particularly across the hippocampus and cerebral cortex (Masters et al., 2015; Sheppard

& Coleman, 2020). This can progress as far as the striatum and thalamus, yet usually sparing the cerebellum (Sheppard & Coleman, 2020). As AD continues to progress throughout the fronto-temporal cortices, neurons in other brain structures begin to be affected and thus further impact other proximal domains of cognition, mood, and behavior (Alzheimer's Association, 2019; Masters et al., 2015; Sheppard & Coleman, 2020). The structure most implicated in AD symptomology is the hippocampus, primarily because the pyramidal cells found in the CA1 region are especially susceptible to cell death; this region is closely associated with the domain of memory (de Flores et al., 2015; Sheppard & Coleman, 2020; Squire & Zola-Morgan, 1991).

Memory functions, and associated impairments, can be partitioned into the processes of encoding, storing, and retrieving information about a specific stimulus. Furthermore, different categories of memories have distinct neuroanatomical and neurophysiological correlates. For instance, explicit and implicit memories seem almost limitless regarding their storage capacities and rely on an intricate neural network throughout the brain. Meanwhile, working memory lasts from seconds to minutes, has a limit to the number of stimuli that can be remembered, and relies on the frontal lobe and the parietal lobe. Declarative memory is composed of semantic memory (context-independent information) and episodic memory (context-specific information). Semantic memory loss typically presents as problems in verbal fluency and naming and can be one of the first cognitive manifestations within the AD continuum (Verma & Howard, 2012). Of these subtypes, working memory and long-term declarative memory are most typically affected early during the AD continuum due to their close association with the hippocampal region (Jahn, 2013). An individual's pattern of memory impairment

depends on the course of AD progression, with structural or functional brain integrity playing a significant role in symptom manifestation (Jahn, 2013). Ultimately the pattern and progression of AD neuropathology along the cognitive continuum impacts the type of memory affected (Jahn, 2013). Importantly, these symptomatic differences can be measured by a variety of neuropsychological approaches and further correlated with neuroimaging biomarkers (Lezak et al., 2012).

Likewise, when examining the relationships between neuroimaging biomarkers and cognitive performance, it is crucial to use a neuropsychological test that best matches the symptomatic domain in question. For example, as AD is primarily responsible for memory loss, the most appropriate tests to measure cognitive impairment in AD would belong to the domain of memory. This is because neuropsychological test construction is typically optimized to best measure the domain of interest, which ultimately maps well to its associated brain region(s). However, as non-amnestic presentations do arise in AD, broader measures of cognition are often seen throughout the literature as well (McKhann et al., 2011). These could range from measures of executive function, to those of language, psychomotor speed, or even simple cognitive screeners (Albert et al., 2011; McKhann et al., 2011; Petersen et al., 2018). One such instance is the measurement of global cognition, often approximated by screening for cognitive status. This is exemplified in the myriad of studies that simply rely on the MMSE, a cognitive screening measure, as an indicator of global cognition or general cognitive status. Although this is a common and quick cognitive measure, this approach limits the quality and specificity of cognitive information that can relate to AD-specific neuroimaging profiles. Instead, a focus on cognitive measures from neuropsychological batteries offers an abundance of

information pertaining to different domain specific deficits and allows for more detailed cognitive-brain correlates.

As AD-specific atrophy often exhibits deficits within the MTL, a focus on the domain of memory allows for a more specialized assessment of brain-cognition relations. Surprisingly, SPARE-AD literature has also primarily relied on MMSE cognitive data, with seldom integration of more robust measures of memory performance from neuropsychological batteries (Da et al., 2014; Davatzikos et al., 2009, 2011; Fan et al., 2008b). Of the memory-based measures, two have been used in the SPARE-AD literature to underscore domain specific associations within this biomarker: the modified Alzheimer's Disease Assessment Scale (ADAS-Cog) and the California Verbal Learning Test (CVLT) (immediate recall and delayed recall tests; Da et al., 2014; Davatzikos et al., 2009, 2011; Fan et al., 2008b). The use of the CVLT measures adequately probe the areas of working memory and delayed recall, which are often impacted first during the AD-pathophysiological process (Jahn, 2013). In fact, targeting domains that show the earliest manifestation of AD-specific atrophy is pivotal to elucidating the progression of AD within earlier phases of the cognitive continuum. This solidifies measures like CVLT, but also suggest the inclusion of measures that test semantic and verbal fluency as well (Jahn, 2013). As the SPARE-AD literature continues to grow, the application of more domain-specific cognitive measures will yield valuable AD-specific cognitive correlates throughout the cognitive continuum that would match nicely with brain-correlates. This proposed study aimed to expand the literature by unifying the brain-correlates and memory-correlates of AD via the SPARE-AD index within a pivotal point in the cognitive continuum of AD-pathophysiology.

Prodromal State

As the AD-pathophysiological process develops on a cognitive continuum, it is important to highlight the different cognitive states an individual may pass through during this process. As stated previously, AD is preceded by a prodromal state. This state can either remain stable, revert to a preclinical phase, or transition into the dementia phase (Albert et al., 2011; Elahi & Miller, 2017; Petersen et al., 2018). A key factor to understanding the conversion of this prodromal state is evidence that suggests the specific brain-cognition correlates found in AD are also observed prodromally, albeit to a lesser degree (Albert et al., 2011; Elahi & Miller, 2017; Petersen et al., 2018). This suggests that the same measures used to identify and diagnose AD (cognitively and pathologically) can be used to predict conversion from the prodromal state to the dementia phase. Ultimately this would provide an avenue for secondary prevention while further elucidating the patterns of AD progression.

Mild Cognitive Impairment and Conversion

When discussing brain-cognition correlates in AD, it is imperative to discuss mild cognitive impairment (MCI) and its role in dementia pathology. MCI is the prodromal profile along the cognitive continuum that is often defined by a marked deficit in one or more cognitive domains that are not as severe when compared to dementia endpoints and with a sparing of instrumental activities of daily living (IADLs) or other aspects of independence (Albert et al., 2011; Elahi & Miller, 2017; Petersen et al., 2018). A key consideration is ruling out the possibility of MCI being caused by other forms of dementia, such as VaD (Albert et al., 2011; Petersen et al., 2018). As such, the NIA-AA workgroups also developed a criterion for diagnosing MCI to due AD. Much like the

criteria for diagnosing probable and possible AD, the guidelines for classifying MCI due to AD can be determined with increased certainty if there is presence of Aβ deposition or evidence of neuronal injury (Albert et al., 2011). In fact, because MCI can be part of the prodromal phase of AD progression, the AD-specific brain correlates discussed previously (see *AD Specific Brain Correlates*) also hold prognostic significance for this state (Albert et al., 2011). That is to say, atrophy of the medial temporal lobe and hippocampal formation would be significant indicators suggesting MCI caused by AD. A caveat to this assumption is that because MCI is a prodromal syndrome it would not be expected to reveal pronounced isocortical neurodegeneration that is typical of more advanced AD pathology (Braak & Braak, 1991; Talwar et al., 2021).

Given the neuroanatomical regions affected by MCI due to AD, it is no surprise that the subtype of MCI that correlates most closely with AD conversion is the amnestic (a-MCI) type, which is primarily defined by deficits in the domain of memory recall and learning (Mitchell & Shiri-Feshki, 2009; Petersen et al., 2018). Furthermore, this intermediate state between normal aging and dementia progression is often considered to be predictive of AD development (Elahi & Miller, 2017; Johnson et al., 2009; Petersen et al., 2018). It is estimated that 15-20% of adults 65 and older have any form of MCI, and that they are more likely to develop AD than those without MCI (Alzheimer's Association, 2019; Roberts & Knopman, 2014). However, exact numbers regarding the conversion from MCI to AD varies depending on methodology. In a random-effects meta-analysis of nine studies examining MCI prognosis, it was revealed that the cumulative incidence for the development of dementia in individuals aged 65 and older with MCI was nearly 15%, after a two year follow-up (Petersen et al., 2018). To probe

MCI conversion rates more accurately, studies integrating highly sensitive and specific AD biomarkers must be prioritized.

The use of the SPARE-AD index has demonstrated a strong predictive value in determining which individuals with MCI convert to AD (Davatzikos et al., 2011). A total of 239 MCI participants from the ADNI were followed for a period of 12 months to determine the ability of SPARE-AD to predict the conversion of MCI to AD, and if this predictive utility increased when integrated with a tau biomarker. An additional aim was to measure longitudinal change of the SPARE-AD index among those that converted against those that did not. As positive SPARE-AD scores reflect AD-like atrophy patterns, it was found that nearly every MCI participant with a positive or near positive SPARE-AD index converted to AD within follow-up (Davatzikos et al., 2011). Those with higher SPARE-AD index scores experienced a more drastic decline in performance on the MMSE at follow-up. Of those that did not convert, about one-third displayed atrophy patterns that approximated AD-like patterns, possibly implying conversion soon after the 12-month follow-up. Those that converted experienced extensive atrophy in the regions of the insula, posterior cingulate, and medial temporal lobe (both grey and white matter) (Davatzikos et al., 2011). Interestingly, this measure demonstrated a slightly higher predictive value than the tau-based CSF biomarker, and the combination of predictors only marginally improved the predictive utility. This is especially surprising given the typically stronger associations between tau-based measures and AD neuropathology (Braak & Braak, 1991; Talwar et al., 2021). In fact, tau biomarkers are typically considered to have more predictive value than measures of neurodegeneration

(Jack et al., 2018). This ultimately highlights the sensitivity and predictive power of the SPARE-AD measure, and its value as an AD biomarker.

A shortcoming of this MCI conversion study is the relatively short follow-up time, which limited the specificity of both biomarkers. Additionally, the presence of white matter atrophy patterns suggests that the algorithm may need to integrate other neuroimaging techniques that are better suited for observing consequences of small vessel disease (Davatzikos et al., 2011). As small vessel disease is found at higher frequencies in African Americans (Barnes et al., 2015; Rahimi & Kovacs, 2014), this study inadvertently provided even more credence for the utility of the SPARE-AD index to probe racial impact on cognitive trajectories in future research. Despite the uncertainty of the specificity of the measure at the time regarding MCI to AD conversion, positive SPARE-AD index scores were still associated with faster decline on the MMSE in individuals with MCI that did not convert to AD (Davatzikos et al., 2011). This suggests that the progressive brain changes marked by SPARE-AD may, in part, underlie faster cognitive decline. This finding emphasizes the utility of SPARE-AD as a predictor of cognitive performance, even in those that are not currently experiencing full AD-like atrophy patterns. The results further frame SPARE-AD as a sensitive AD-specific biomarker that may be applicable to the tracking of cognitive trajectories that deviate from normal aging within preclinical populations.

Preclinical AD State

According to the conceptualization of AD via the guidelines proposed by the NIA-AA workgroup, preclinical AD is the initial profile of the AD-pathophysiological process (Sperling et al., 2011). It is an asymptomatic phase of AD in which the individual

does not have the cognitive symptoms of either MCI or dementia and can potentially last up to 20 years (Alzheimer's Association, 2021; Jack et al., 2018; Sperling et al., 2011). Given this premise, in terms of primary prevention for the AD-pathophysiological process, the preclinical phase would be the ideal target to begin prophylactic treatment. In fact, it appears that the push to find primary and secondary prevention strategies may be what motivated the NIA-AA workgroups to facilitate a paradigm shift towards the cognitive continuum model and expand the importance of transitioning through the preclinical, prodromal, and dementia states of this continuum (Jack et al., 2018; Sperling et al., 2011). The foundation of the preclinical phase is the asymptomatic accumulation of Aβ deposition and the sequential impact this accumulation has on the brain prior to the development of frank cognitive impairment (Jack et al., 2018; Sperling et al., 2011).

The sequential pathway for this cognitive continuum is as follows: 1.) Normal State (i.e., before AD pathophysiological process begins), 2.) preclinical amyloidosis 3.) amyloidosis with neurodegeneration, 4.) amyloidosis with neurodegeneration and mild cognitive decline, 5.) MCI due to AD (precipitated by both amyloidosis and neurodegeneration), 6.) early clinical AD, and 7.) advanced clinical AD presentation (Jack et al., 2018; Sperling et al., 2011). In terms of adequate biomarkers for the preclinical state, the same strategies measuring amyloid, tau, and pre-symptomatic neurodegeneration (see *AD-Specific Brain* Correlates) are typically employed during the suspected preclinical amyloidosis and both of the amyloidosis with neurodegeneration phases. Due to the lack of symptoms and the burgeoning biomarker studies in preclinical timepoints, there has been a dearth of prevalence estimates for preclinical AD (Alzheimer's Association, 2021; Brookmeyer et al., 2018).

Currently one systematic review has reported a method that uses past AD epidemiological incidence, mortality, and projection data to forward calculate in a multistate model, the prevalence of preclinical AD (Brookmeyer et al., 2018). The authors also developed an additional model to supplement the cognitive continuum, wherein the normal state is followed by direct neurodegeneration without the presence of amyloidosis (Brookmeyer et al., 2018). This neurodegeneration phase then proceeds to the MCI phase and the subsequent AD phases. The rationale behind this perspective comes from findings of neurodegeneration in cognitively normal persons with preclinical AD that did not experience abnormal rates of Aβ deposition (Knopman et al., 2013). This perspective highlights the importance of neurodegeneration as a biomarker and reinforces its predictive utility in the AD pathophysiological process. Each phase of both preclinical pathways were then used to calculate prevalence by age and gender and forecast up until calendar year 2060 (Brookmeyer et al., 2018). This method estimated a total of 46.7 million preclinical individuals in the U.S. during 2017—22.14 million with amyloidosis, 8.33 million with only neurodegeneration, and 16.23 million with both amyloidosis and neurodegeneration, and forecast a total of 75.68 million by 2060. These prevalence estimates reinforce the importance of neurodegeneration as a biomarker for preclinical AD as more than half of the estimated preclinical population is presumed to have some degree of neurodegeneration. This further solidifies the need to analyze neurodegeneration patterns within preclinical samples to predict AD outcomes and trajectories. Before delving deeper into the neurodegeneration findings within the preclinical phase, it is important to contextualize preclinical AD within the context of normal aging and additional disease processes.

As people age it is typical to observe a gradual yet normative cognitive decline among individuals after reaching their peak of neurobiological and cognitive maturation (Anstey et al., 1993; Harada et al., 2013). There is evidence that certain elements of cognitive functioning such as vocabulary and crystallized intelligence may improve with age while the domains of processing speed, memory, and conceptual reasoning tend to decline with age (Harada et al., 2013; Salthouse, 2019). Similarly, even brain changes—specifically atrophy—have been seen in healthy adults without signs of accelerated aging or a preclinical dementia process (Resnick et al., 2003). In a longitudinal study involving 92 older adults from the BLSA, MRI scans were gathered over the course of four years. The predominately White sample (mean age = 74, mean education = 16 years) received scans at baseline, at a two-year follow-up, and a four-year follow-up (Resnick et al., 2003). Within this sample, a subset of 24 participants without any medical conditions or impairments (dubbed the very healthy group) were observed. Among the main sample and the subgroup, total brain, white matter, and gray matter loss was observed, as well as an increase in ventricle size (Resnick et al., 2003). Although a shortcoming of this study was that it did not track cognition with each follow-up, it still showcases that even in purportedly healthy aging, slight neuronal loss over time is still expected.

Despite an expected change in brain and cognitive outcomes from normal aging, a plethora of environmental, genetic, and ethno-racial factors can impact the rate of decline and increase the risk of cognitive impairment or developing dementia (Anstey et al., 1993; M. E. Levine et al., 2018; Steenland et al., 2014). This is, at least in part, because aging can be divided into two distinct categories: primary and secondary aging. Primary aging involves the innate maturational processes of an individual and secondary aging

comprises of the effects of environment and disease (Anstey et al., 1993). As a whole, cognitive decline reflects a continuum of cognitive changes, some of which may be associated with aspects of normal aging, whilst others are associated with a more accelerated form of secondary aging. This accelerated aging can lead to steeper rates of cognitive decline and ultimately to a state of impairment. Currently, it is a substantive challenge to differentiate between preclinical AD, early signs of different dementia processes (such as VaD), and accelerated aging caused by secondary aging factors, some or all of which may overlap. This is likely, in part, because vascular risk factors can accelerate the progression of AD in individuals with a preclinical or MCI neuropathology (Brookmeyer et al., 2018; Rahimi & Kovacs, 2014). This results in a difficulty to parse out the effects of vascular pathology from those of preclinical AD pathophysiology, and a need to further validate the biomarkers implicated in preclinical AD (Alzheimer's Association, 2021; Brookmeyer et al., 2018). One such biomarker that has held promise in maintaining high sensitivity to AD-like atrophy patterns across the cognitive continuum is the SPARE-AD measure (Davatzikos et al., 2009, 2011).

Early in its inception, the high-dimensional pattern classifier that served as the foundation for SPARE-AD was used as a tool to better ascertain differences between cognitively normal (CN), MCI, and AD patterns of atrophy in the ADNI (Fan et al., 2008). This approach included 66 CN individuals (essentially a preclinical sample), 88 MCI patients, and 56 AD patients. Beyond simple group analyses, this study probed individual patient analysis with the aim to classify individual scans belonging to preclinical, MCI, or AD participants. This classifier compared the profiles of those with AD and those with MCI against the CN participants and found the classification accuracy

to be 94.3% when discerning the atrophy pattern of the preclinical group from AD participants and 81.8% when comparing the preclinical group from the MCI group (determined via the leave-one-out cross-validation method; Fan et al., 2008). Meanwhile ROI volumetric analysis only had a classification accuracy of 82.0% for the AD vs. preclinical comparison and 76.0% for the MCI vs. preclinical comparison (Fan et al., 2008). This result not only underscores the accuracy of the pattern classification system used by SPARE-AD, but also makes it clear that there are discernable patterns of neurodegeneration within preclinical participants that can be used to differentiate the phases across the AD cognitive continuum.

These findings were most easily visualized within the MCI group, which had significant temporal lobe atrophy (primarily in the hippocampus, superior, inferior temporal gyrus, and uncus) as well as medial GM atrophy (within the posterior cingulate, adjacent precuneous, and the medial aspect of the uncus; Fan et al., 2008). This is in contrast with typical MRI findings for MCI that focus only on the MTL structures when observing MCI related atrophy (Albert et al., 2011). This more extensive neurodegeneration pattern seems to imply that the majority of MCI patients may have more of an AD-like structural profile than previous literature seems to suggest. This further reinforces the limitations of ROI-focused approaches as the need for *a priori* decisions on which structures to observe could have caused the extent of the current pattern of atrophy to go completely unnoticed. These findings additionally suggest that more emphasis should be placed on studying the atrophy patterns within preclinical groups, as the neurodegeneration pattern of this group is so dissimilar to either the MCI

or AD groups. This sets the stage for using spatial atrophy patterns as biomarkers in preclinical populations to predict future neurodegeneration.

Following this thread, the classification algorithm was built upon when applied to the BLSA and used to assess progression of preclinical atrophy patterns via SPARE-AD index scores (Davatzikos et al., 2009). This study used MRI scans from 109 CN participants and 15 MCI participants from the BLSA to evaluate AD-like atrophy patterns longitudinally and relative to performance on the MMSE and CVLT (Davatzikos et al., 2009). As expected, the vast majority (105 subjects) of CN participants had SPARE-AD patterns that matched typical brain morphometry (Davatzikos et al., 2009). After the SPARE-AD scores were separated into the top quartile and the lower 75%, those with higher SPARE-AD index scores had worse performance on the CVLT immediate recall, delayed recall, and MMSE during the first visit but not the last visit. What is integral to note from these findings is that although preclinical AD is—by definition—absent of cognitive impairment, it apparently can still present cross-sectionally as a lower baseline cognitive performance for those at risk of future decline or those who transition into MCI.

Prospectively, the annual rate of change in SPARE-AD index scores for the CN participants significantly increased over time, which underscores the impact age has on the AD-pathophysiological process. For the majority of these individuals, although the rate of change increased over time, the SPARE-AD index remained negative (i.e., aligned with CN patterns) and showed a stable longitudinal progression. When probing the relation between rate of SPARE-AD change and cognition, it was determined that those with rates of change in the upper quartile also had lower performance on CVLT

immediate recall, delayed recall, and MMSE measures compared to those in the lower 75% (Davatzikos et al., 2009).

In terms of observed atrophy patterns, those CN in the top quartile of SPARE-AD index further showed less grey and white matter volumes compared to those in the lower 75% (Davatzikos et al., 2009). Additionally, as regions of abnormal white matter on T_1 images appear dark and are typically segmented as grey matter, the posterior periventricular regions within the top quartile of SPARE-AD index scores appeared to have more grey matter tissue, thus indicating increased abnormal white matter tissue that merely presents as grey matter in T_1 imaging (Davatzikos et al., 2009). This abnormal white matter around the ventricles is typically a sign of small vessel disease that is often found in older individuals (Davatzikos et al., 2009). Being able to differentiate between grey matter and abnormal white matter (that is segmented as grey matter) is an example of how the SPARE-AD index, facilitated by supervised classification methods, is able to discern between AD-specific neurodegeneration and lesions typically associated with VaD pathology. This is also crucial for studying populations that are vulnerable to small vessel disease, such as African Americans (Barnes et al., 2015).

Interestingly, of the 4 CN subjects that had positive SPARE-AD scores, there was an overall reduction of size in the temporal lobe, which matches the typical neuropathological progression of AD. These 4 CN subjects are interesting because even though they had a more AD-like pattern of atrophy, they did not meet the criteria for MCI or AD. This may suggest that another AD-specific biological factor exacerbated the neurodegeneration profile of these subjects. One underlying biological factor that is highly associated with the likelihood of AD progression is mutations or variants in genes

that drive neuronal integrity, growth, and development. The proposed study aimed to further the prior literature by integrating the SPARE-AD neurodegenerative profile with a highly validated genetic risk factor for AD-pathophysiology to generate a more robust model of cognitive and brain outcomes in a preclinical sample.

Genetic Underpinnings of AD

Regarding non-imaging based biomarkers, there is an increased level of certainty for a probable AD diagnosis if the individual is a carrier for a causative AD genetic mutation, primarily in the Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and the amyloid precursor protein (APP) genes (McKhann et al., 2011). This is because in terms of etiology, it has been found that over 95% of AD is sporadic while a miniscule percentage is autosomal-dominantly inherited through the mutations in these genes. The vast majority of familial variant AD cases have an early-onset, at approximately 45 years-old, while most sporadic AD cases have a late-onset with a mean age of 80 years-old (Masters et al., 2015; Sheppard & Coleman, 2020). It is for this reason that a large body of AD research has focused on understanding the genetic underpinnings and complexities associated with the development of AD as well as their impact on preclinical cognitive performance.

This approach has been especially fruitful for the familial variant of AD, where these specific genetic mutations nearly guarantee the development of this neurodegenerative disease (Elahi & Miller, 2017; Masters et al., 2015; Tanzi, 2012). These genes are involved in the pathway leading to the creation of amyloid-beta. Mutations in these genes cause excess production of the amyloid-beta protein and inevitably lead to dementia in these cases. One isoform of amyloid-beta in particular, the

42 amino acid Aβ ($A\beta_{42}$), is most prone to Aβ aggregation and linked with AD development. The 200+ possible mutations in these three specific genes are known to severely augment the ratio of $A\beta_{42}$ in the brain and cause the accumulation of amyloid fibrils, associated with early-onset neurodegeneration (Tanzi, 2012). Additionally, the type of gene mutation and its respective $A\beta_{42}$:$A\beta_{40}$ ratio is known to predict the mean age of onset for this form of dementia (Masters et al., 2015). Despite the strong link between these genes and AD, their impact is only seen in the familial and early-onset variants; which account between 1-5% of all AD cases (Alzheimer's Association, 2019; Elahi & Miller, 2017; Tanzi, 2012).

In sporadic AD, the genetic underpinnings are far more complex and involve mechanisms that are much harder to elucidate. Of the countless genome-wide association studies related to AD, over 20 genetic risk loci were identified with modest individual and population level effect sizes (Elahi & Miller, 2017; Van Cauwenberghe et al., 2016). These associated genes are often implicated within the Aβ hypothesis of AD pathology; however, as one teases apart the literature it becomes evident that these associated genes can actually be sorted into three distinct physiological pathways (Van Cauwenberghe et al., 2016). These genes contribute to the immune system and inflammatory response, endosomal vesicle cycling, and/or cholesterol and lipid metabolism pathways (Van Cauwenberghe et al., 2016).

A promising gene associated with MCI and high AD risk susceptibility is the complement component (3b/4b) receptor 1 (CR1), which is integral in mediating innate immunity (Lambert et al., 2009; Van Cauwenberghe et al., 2016; Varatharajah et al., 2019). This is a gene that is closely tied with activating the complement system, which is

responsible for producing proteins that enhance phagocytosis and clearing the body of damaged cells and is expressed throughout neurons and glia in the brain (Karch & Goate, 2015; Lambert et al., 2009). Mutations in CR1 are associated with its ability to clear the brain of $A\beta_{42}$ and neuritic plaques (Karch & Goate, 2015; Lambert et al., 2009). In fact, a recent machine-learning approach focused on understanding the progression from MCI to AD found that expression of CR1 was not only essential in predicting conversion to AD, but also elucidated the speed and rate of progression (Varatharajah et al., 2019). A gene that is also associated with the complement system, but works via a different mechanism, is the apolipoprotein known as clusterin (CLU); which works through cholesterol metabolism and apoptosis (Karch & Goate, 2015; Lambert et al., 2009). CLU was the first novel gene target in GWAS, is abundantly found in amyloid plaques, and tied to white matter integrity (Karch & Goate, 2015; Sapkota & Dixon, 2018; Van Cauwenberghe et al., 2016). Similarly, the Phosphatidylinositol binding clathrin assembly protein (*PICALM*) gene is also associated with clearing the brain of $A\beta_{42}$ but is involved in endocytosis—the process in which matter is carried in to cells (Harold et al., 2009; Karch & Goate, 2015). PICALM is most heavily expressed in neurons and is also involved in synaptic vesicle fusion and APP trafficking (Karch & Goate, 2015; Sapkota & Dixon, 2018). Certain variants of this gene significantly impact the default mode network in those with MCI and results in greater susceptibility to episodic memory impairments (Sun et al., 2017). All three of these genes are not only implicated in AD development, but are also associated with developing MCI and accelerated cognitive decline in healthy aging adults (Cruz-Sanabria et al., 2020; Karch & Goate, 2015; Sapkota & Dixon, 2018).

However, out of all the genetic risk loci discovered and studied via genome-wide association studies (GWAS), none is more heavily associated with AD and MCI than the APOE gene, particularly the variant responsible for the ε4 allele (Elahi & Miller, 2017; Masters et al., 2015; Van Cauwenberghe et al., 2016). Not only is this gene among the strongest predictors of AD pathology, but it is also predictive of MCI and the rate of cognitive decline in aging populations. This variant has also been implicated to interact synergistically with other genes such as CR1, CLU, and PICALM to further increase the likelihood of AD progression and exacerbate their influence on cognitive aging (Sapkota & Dixon, 2018; Thambisetty et al., 2013). This is why APOE is often the most cited and researched gene associated with AD pathology (Alzheimer's Association, 2019). This also showcases the multifactorial approach and body-wide interactions among genes that are involved in AD pathology. Ultimately, AD is not only a disease of the brain and cognition, but one that is impacted by a variety of risk factors across the spectrum of health and aging. The study of APOE specifically allows for a refined approach to elucidating the genetic mechanisms driving neuroanatomical and cognitive outcomes, which further strengthened this proposed study.

APOE and AD

To understand the impact of APOE on AD and cognitive performance, it is first imperative to understand the physiological role of this gene. The APOE gene is found on chromosome 19 and encodes a plasma protein responsible for various functions, primarily in lipoprotein metabolism and lipid transport (Mahley, 1988; Masters et al., 2015; Tanzi, 2012). Initial reports linked APOE to AD by genetic linkage of the disease to chromosome 19 as well as determining APOE immunoreactivity in Aβ deposits

(Masters et al., 2015; Tanzi, 2012). This highlighted the genetic and functional associations between APOE and AD, which resulted in a boon of research surrounding this gene and making it an established AD risk factor (Tanzi, 2012). APOE mRNA is found in largest quantities within the liver, followed by the brain (Mahley, 1988). This gene is highly expressed in astrocytes and microglia, and is also the major apolipoprotein of the cerebrospinal fluid (CSF) (Mahley, 1988; Masters et al., 2015). The protein encoded by APOE binds to Aβ and is also involved in neuronal growth and the clearing of the Aβ aggregates in the brain (Lambert et al., 2009; Masters et al., 2015; Tanzi, 2012). This accumulation of Aβ, as discussed previously (see *AD Specific Brain Correlates*), impacts brain integrity, and is hypothesized to begin the cascade of neuroanatomical consequences responsible for AD-related cognitive decline.

This gene has three major isoforms that come from three alleles: ε2, ε3, and ε4 (Mahley, 1988). The ε4 allele exhibits normal receptor binding but still is associated with elevated low-density lipoprotein (LDL) and elevated plasma cholesterol (Mahley, 1988). It is this allele that is the most associated with elevated risk for AD development. In fact, estimates suggest that this allele contributes to 50% of sporadic AD (Masters et al., 2015). The odds of AD is three-fold for those that are heterozygous for the APOE ε4 allele, while homozygosity for the APOE ε4 allele is associated with a 10-15 fold increase in likelihood of developing AD (Elahi & Miller, 2017; Masters et al., 2015; Tanzi, 2012; Van Cauwenberghe et al., 2016). On the other hand, the ε2 allele demonstrates protective effects, with lower quantities of Aβ deposits and the ε3 allele is considered neutral in terms of AD risk (Masters et al., 2015; Sapkota & Dixon, 2018). Although the ε4 allele is the strongest predictor of sporadic AD, unlike early onset and

familial variants of AD, this genetic locus is not sufficient to fully explain or cause AD on its own (Farrer et al., 1997; Van Cauwenberghe et al., 2016). Because of this, research has sought to elucidate not only how the ε4 allele contributes to AD pathogenesis, but what factors interact with this genetic risk factor that could either exacerbate or ideally ameliorate its pathology.

The APOE ε4 allele is highly linked with vascular contributions to cognitive impairment and dementia (Duong et al., 2021; Pendlebury et al., 2020). One proposed mechanism in which this occurs is through the metabolism of cholesterol in the body. The accumulation of cholesterol and other lipids leads to a chronic dysfunction of lipid homeostasis and the formation of plaque in blood vessels known as atherosclerosis—a subclinical CVD that is linked to cognitive impairments, structural changes in the brain, and accelerated cognitive decline (Chen et al., 2017; Duong et al., 2021; Palta et al., 2019; Wendell et al., 2016). In fact, a meta-analysis of 490 case-control studies demonstrates that APOE ε4 carrier status is also associated with elevated risk for intracranial atherosclerosis (Wei et al., 2017). Furthermore, the ε4 allele specifically disrupts lipid metabolism which promotes atherosclerosis and may even modulate tau neuropathology (Duong et al., 2021). This could also provide a rationale for why AD and VaD is the most common form of mixed dementia: the very molecular basis of AD progression is tightly linked to the etiological factors that influence vascular-driven impairments. Interestingly, epidemiological studies show that African Americans typically have better cholesterol profiles than Whites (Lin et al., 2011; NCEP, 2002; Waldstein et al., 2016); yet a higher frequency of the ε4 allele (Maestre et al., 1995; Mayeux et al., 1993; Tang, 1998). This begins to suggest pathways through which the

impact of APOE ε4 may differ across race and subsequently impact brain health and cognitive endpoints outside of the typical amyloid-hypothesis.

APOE and MCI

Not only is APOE ε4 linked to AD pathology and CVD risk factors, but it is also closely associated with the incidence of MCI and accelerated cognitive aging in healthy adults (Elias-Sonnenschein et al., 2011; Kryscio et al., 2006; Varatharajah et al., 2019). In a 16-year longitudinal study of healthy adults, it was found that the APOE ε4 allele conferred an increased risk of MCI incidence up to 1.4-fold compared to non-carriers (Boyle et al., 2010). In a study looking at early MCI, it was further noted that APOE ε4 carrier status was associated with higher amyloid accumulation and lower Aβ in the CSF in these prodromal states (Risacher, 2013). This aligns with neuropathological data that suggests amyloid plaque can precede symptoms of AD. Interestingly, in a meta-analysis of 35 prospective cohort studies, having at least one APOE ε4 allele status conferred only a moderately increased risk for conversion from MCI to AD (Elias-Sonnenschein et al., 2011). This meta-analysis totaled 6,095 subjects and ultimately demonstrated a twofold increased risk of progression from MCI to AD in heterozygotes and a fourfold risk for homozygotes of the APOE ε4 allele compared to non-carriers (Elias-Sonnenschein et al., 2011). This reinforces the role APOE ε4 plays on not only the progression towards AD, but the rate in which cognitive decline occurs.

In a more recent longitudinal cohort study, it was determined via Cox proportional-hazards models controlling for age, sex, education, baseline cognitive status, and years of initial visit in an all-White sample, that homozygous APOE ε4 carriers had a 153% increased risk of MCI compared to ε3 homozygotes (Ren et al., 2020). In this same

study, the incidence of MCI at 5-years was 36% for the homozygous ε4 carriers and 30% for ε3 homozygotes, while at the 10-year follow-up the incidence of MCI was 54% for the homozygous ε4 carriers with only 37% for the ε3 homozygotes. This reinforces that homozygosity for ε4 confers the highest MCI incidence rate among all allele combinations (Ren et al., 2020). However, due to the complex and study-specific nature of assessing MCI, it is often difficult to pinpoint risk factors that contribute to the emergence of this impairment. In fact, associations between APOE ε4 carrier status and a-MCI can vary in significance depending on neuropsychological impairment definitions even within the same dataset (Jefferson et al., 2015). When using a traditional education and age adjusted normative definition of impairment, APOE ε4 carrier status was not associated with a-MCI; yet when using an impairment definition based on performance standardization from the Wide Range Achievement Test-3 and age, this association was significant (Jefferson et al., 2015). This emphasizes the importance of using refined and performance-based definitions of impairment for tracking associations between the APOE ε4 allele and cognitive outcomes. This is because neuropsychological batteries and cognitive tests map closely to domain-specific neuroanatomic endpoints and provide a strong basis for understanding impairment and dementia. It is these associations in MCI, cognitive aging, and ultimately AD progression that motivate research to further explore the impact APOE ε4 carrier status has on not only cognitive domains but neuroanatomical end-points.

An example of this is the integration of SPARE-AD and APOE in the prediction of MCI to AD conversion (Da et al., 2014). It was determined that SPARE-AD had a comparable predictive value to the ADAS-Cog in predicting conversion of MCI to AD

(Da et al., 2014). However, the addition of APOE ε4 status to the SPARE-AD index significantly improved the prediction of the time to conversion (Da et al., 2014). Additionally, this marker demonstrated strong sensitivity and specificity in a 10-fold cross-validation and an area under the curve of 0.98 (Da et al., 2014). This highlights the synergy between SPARE-AD and the impact of the APOE ε4 allele in predicting accelerated cognitive decline within the prodromal state and the trajectory toward the dementia state. Another interesting finding from this study was that, in a subgroup of patients that had MCI and amyloid biomarker data, SPARE-AD was able to predict conversion to AD in individuals that had normal levels of amyloid (Da et al., 2014). This finding provides further evidence of the possibility that manifestations of neurodegeneration precede amyloidosis, implying that early neuroanatomical profiles of individuals may offer predictive utility with respect to AD pathology even in the absence of abnormal $A\beta_{42}$ aggregation. These findings support the current proposal's design in probing relations of APOE to SPARE-AD in a preclinical sample.

APOE and Preclinical Brain Outcomes

As of 2017, the estimated prevalence of preclinical AD individuals in the U.S. experiencing signs of neurodegeneration was 24.56 million and counting (Brookmeyer et al., 2018). As APOE ε4 carrier status is one of the strongest genetic risk factors for AD progression, it seems likely that among these estimated millions, a subset would be carriers of the ε4 allele. In fact, given the biological role the ε4 allele has on Aβ and neuronal growth, it would also be reasonable to predict that the presence of neurodegeneration within the estimated preclinical population is driven, in part, by those that are APOE ε4 carriers. It was further estimated that the U.S. has 38.37 million

preclinical individuals experiencing amyloidosis (Brookmeyer et al., 2018). Since the ε4 allele is intricately tied to the amyloidosis mechanism, there is further credence in the logic that the ε4 carrier status is greatly influencing, if not partially explaining, the neuroanatomical profile of a large proportion of those in the preclinical AD state.

Although much of the same techniques used to measure AD-specific brain correlates (amyloid PET, tau-based PET, and structural MRI) are used to gather neuroimaging biomarker data in preclinical samples, few studies have explored the relation of these biomarkers to genetic risk factors in this population. This may be due to the fact that genetics is not formally included in the NIA-AA research framework (Sperling et al., 2011). The cognitive continuum of AD-pathophysiology is based on the concept that disease rests on neuropathologic change, and thus must be detected by in vivo imaging biomarkers (Jack et al., 2018; Sperling et al., 2011). As gene variants do not explicitly measure pathologic change, and instead only provide information on overall risks for the development of pathologic change, they are not actively prioritized within this neuropathological-centric research framework (Jack et al., 2018; Sperling et al., 2011). The ε4 allele in particular provides a mechanistic explanation for the presence of Aβ deposits and the process of amyloidosis but does not actually measure the presence of Aβ accumulation or delineate where on the AD continuum a particular individual would fall. This is a major oversight within the literature as those that do incorporate the ε4 allele in neuroimaging studies ultimately strengthen the predictive patterns of current biomarkers and elucidate novel views on preclinical prevalence.

In fact, this notion is supported by two population-based studies which probed the role of APOE status on age and sex specific frequencies of amyloidosis and

neurodegeneration from the Mayo Clinic Study of Aging (Jack et al., 2014, 2017). In a cross-sectional analysis of 985 cognitively normal subjects ranging from 50-89 years-old, structural MRI and PET neuroimaging was conducted to determine presence of amyloidosis (A+ vs A-) or neurodegeneration (N+ vs N-) (Jack et al., 2014). The subjects were age and sex stratified, and placed in one of four possible neuroanatomical profiles: A−N−, A+N−, A−N+, or A+N+ (Jack et al., 2014). Associations between APOE ε4 carrier status and these neuroimaging profiles were evaluated to understand the prevalence of amyloidosis and neurodegeneration among carriers. The presence of amyloid and neurodegeneration was higher at older ages and modified by APOE ε4 status, with carrier status conferring higher likelihood of amyloidosis across the stratified ages, but increasingly so with greater age (Jack et al., 2014). This falls in line with recent meta-analysis findings that have demonstrated CN homozygous APOE ε4 carriers to experience amyloidosis as early as 40-years old (Jansen et al., 2015). As age is the primary risk factor for AD, the increased rate of onset moderated by ε4 is striking and clinically relevant.

Those that carried this allele most frequently fell in either the A+N+ or the A+N− profile and least frequently had the A-N+, which aligns with this allele's role in Aβ deposition. This methodology was expanded upon a few years later by incorporated tau-based PET biomarkers and developing A(amyloid) T(tau) N (neurodegeneration) profiles. Similarly, ε4 carriers were nearly twice as frequent among A+ profiles compared with A− groups. These approaches provided information regarding typical brain profiles of APOE ε4 carriers, which is predominately based on the increase of amyloidosis. The overall drawback regarding this approach is that the neuroimaging in these studies still relied on

determining manual cutoff points and ROI based neurodegeneration patterns, instead of machine learning strategies of AD-specific atrophy. It seems however, that the majority of APOE-brain literature suffers from these methodological limitations.

A review of AD neuroimaging biomarkers in CN ε4 carriers revealed a dose-dependent trend pertaining to structural MRI and PET imaging outcomes whereby homozygous carriers had more profound profiles of neurodegeneration and Aβ deposition than heterozygous carriers or non-carriers (Chételat & Fouquet, 2013). In preclinical carriers, neurodegeneration affects regions most susceptible to AD-pathology (such as those found in the MTL) while this pattern is not seen in non-carriers. In reviewing the structural MRI literature, it appears that the influence of APOE ε4 may be more subtle than the findings of amyloid PET imaging (Chételat & Fouquet, 2013). This is somewhat intuitive given the direct role of ε4 on Aβ, and the rather indirect role it has on neurodegeneration. Interestingly, this review calls for comparing neuroimaging data between carriers and non-carriers, so that one might be able to detect potential early neuroimaging biomarkers of AD that would be present in the asymptomatic state (Chételat & Fouquet, 2013). This methodology could hold promise in further elucidating the unique patterns of preclinical brain profiles; however, using simple ROI-based structural MRIs or relying on Aβ deposition would not be robust enough imaging endpoints. This is where a shift towards advanced neuroimaging techniques like SPARE-AD can further elevate the literature pertaining to ε4 associations with neuroanatomical profiles. The SPARE-AD index has a higher sensitivity than these other measures and may be able to elucidate the impact ε4 carriership has on neurodegeneration profiles by assessing an AD-specific pattern of brain atrophy and potentially providing a key

mechanism through which this allele affects cognition. The proposed study examined, for the first time, whether SPARE-AD mediates the relation between ε4 status and early AD-related cognitive correlates in a preclinical sample.

APOE and Preclinical Cognitive Outcomes

As carrier status for the ε4 allele seems to impact preclinical brain-correlates, so too does it impact cognitive trajectories. This is primarily because changes in neuropathologic outcomes, particularly those involved in neurodegeneration, may precipitate cognitive changes downstream (Hampel et al., 2008). Although by definition, preclinical populations cannot have evidence of impaired cognition, there are several factors that can influence preclinical populations to have lower level of cognitive function (or poorer trajectories) based on AD-pathophysiology (Jack et al., 2018; Sperling et al., 2011). Furthermore, the focus on preclinical cognitive outcomes, particularly in relation to APOE, is ideal for the goal of developing targeted primary prevention interventions (Jack et al., 2018; Sperling et al., 2011).

To this end, an early cross-sectional study examining the impact of the ε4 allele on cognitive outcomes was conducted on a sample of 220 White middle-aged preclinical sample (Flory et al., 2000). In this study, cognition was determined via neuropsychological testing which focused on the domains of memory and attention. The attention tests used were the Digit Span Forward and Backward (longest span), and the Recurring Words (%correct) test; while the memory domain relied on the Digit Symbol recall, Figure Delayed Recall test, Verbal Learning Total, and Verbal Learning Delayed Recall (Flory et al., 2000). This model also probed moderation by sex and further adjusted for age, education, income, and estimated WAIS-R IQ; however, education and

income were dropped from the analyses due to not being significantly associated with the dependent measures (Flory et al., 2000). It was documented that the ε4 allele was significantly associated with significantly diminished performance in the domain of memory. In contrast, genotype had no impact on attention measures and no Genotype × Sex interactions were present. Of note is that this was the first study to observe reduced memory performance in a preclinical sample younger than 60 years (Flory et al., 2000). This pattern potentially speaks to the predictive nature of ε4, whereby the lower memory performance in preclinical carriers likely presages more notable declines in cognition and more rapid neuroanatomical changes (Flory et al., 2000; Jansen et al., 2015). This highlights the importance of probing preclinical associations in middle-aged cohorts and the impact the ε4 allele has on cognitive performance. A major limitation of this study however is that the sample was comprised solely of Whites, which limits its generalizability and further emphasizes the need for studies to examine more diverse samples to get a better understanding of the impact of the ε4 allele.

To gather a better sense of this impact, a meta-analysis further probed the role of the ε4 allele on preclinical cognitive outcomes and additionally examined effect sizes and possible moderating variables for this relation (Wisdom et al., 2011). A total of 77 studies, representing 40,942 cognitively healthy adults were included in this analysis (Wisdom et al., 2011). In analyzing the available data, this study found that ε4 carriership negatively impacted performance on measures of episodic memory, executive functioning, and overall global cognitive ability (Wisdom et al., 2011). A small effect size was also present for the allele's impact on the domain of perceptual motor speed. This highlights the cognitive domains affected by the ε4 allele and may allow for further

differentiation between AD pathology and that of other dementias. The findings also reinforce the need to focus on sensitive neuropsychological tests and to deviate from global measures of cognition, as AD-pathophysiology has a distinct pattern of cognitive impact. This meta-analysis also probed the role that age and zygosity had on these domains and found that older age generates a larger gap between ε4 carriers and non-ε4 carriers on measures of episodic memory and global cognitive ability. Despite this, the meta-analysis failed to probe race as a potential moderator. This limitation is primarily due to most preclinical studies relying on predominately White samples and having a limited sample size of African American participants to fully probe the relation of race and ε4 on cognitive performance. Nonetheless, results of this meta-analysis support the significant relation of this allele to cognitive outcomes, which is crucial to understanding the trajectories and risk of cognitive decline along the cognitive continuum of AD-pathophysiology.

Despite this analysis, a more recent review of the literature documents inconsistencies in the ε4-cognition literature that warrant further exploration (O'Donoghue et al., 2018). Over the past 20+ years of literature probing these associations, a definitive pattern has failed to emerge due to some studies finding ε4-cognition associations and others finding no association (O'Donoghue et al., 2018). These authors suggested that methodological limitations may explain the heterogeneity in ε4-cognition findings; these include small sample sizes, reliance on older adult samples, inappropriate cognitive measures, and a lack of identifying relevant moderators as being major factors (O'Donoghue et al., 2018). Adequate sample size is important in ensuring statistical power for the examination of these associations. In terms of age, it is the

principal risk factor for AD, and older individuals are more likely to have an accumulation of AD pathology and transition into the prodromal state. In older adult samples it is difficult to disentangle the potential subtle impact of the prodromal state on cognition, even when screening for MCI (O'Donoghue et al., 2018). Thus, to observe the effect of the ε4 allele on cognitive outcomes in a truly preclinical sample, older adult samples may be inappropriate to do so given the potential confounding of subtly accumulated prodromal effects. Furthermore, studies in adolescents and young adults have shown antagonistic pleiotropy—where the impact of a gene is advantageous in early life but deleterious in later life—regarding ε4-cognition associations (O'Donoghue et al., 2018). This reinforces the need for a focus on middle-aged samples.

In terms of cognitive measures, many lack sensitivity or specificity to subtle variations in cognition or changes in specific domains, and thus the critical role of domain-specific neuropsychological batteries is emphasized here. In those studies that used neuropsychological batteries instead of a single test, it was found that ε4-cognition associations were noted in some, but not all, domains of cognition (O'Donoghue et al., 2018). This gives further credence to the importance of AD-specific cognitive correlates rather than global cognitive screeners. Interestingly, this review fails to address racial disparities in the ε4-cognition literature, and the potentially differential impact the ε4 allele may have on cognition in this context. It is this emphasis, combined with addressing methodological limitations of prior studies, that allowed the current proposed study to add to the preclinical ε4-cognition literature.

The O'Donoghue and colleagues (2018) review further indicated the overwhelming need to examine the ways in which the ε4 allele affects neurobiological

processes to impact cognitive consequences in preclinical samples. In that regard, it has further been suggested that an emerging pattern of potentially amyloid-independent mechanisms directly impact cognition in the preclinical state, by increasing vulnerability to neuroanatomical changes, in addition to exacerbating the effects of Aβ deposits and neuronal loss in the brain (Lim et al., 2015; Mormino et al., 2014; O'Donoghue et al., 2018). This pathway is especially important when attempting to predict the conversion from a preclinical state to MCI and in determining overall AD risk. Unfortunately, few preclinical studies properly track the rates of change in cognition or determine neurodegenerative factors that accelerate the conversion to the MCI phase within the cognitive continuum.

In a study that tracked preclinical population outcomes longitudinally, data from 490 CN older adults were collected from the Harvard Aging Brain Study, the ADNI, and the Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBLS; Mormino et al., 2014). With a median follow-up period of nearly 1.49 years across the three studies, the impact of carrier status and Aβ were tracked and examined against performance on select neuropsychological tests. Given the limited overlap in measures of cognition across studies, cognitive decline was assessed via performance on the MMSE and the immediate and delayed recall scores from the Logical Memory test; while Aβ was measured via amyloid PET and divided into two groups (a high Aβ deposition group and low Aβ). Those with higher Aβ deposition were more likely to be ε4 carriers than those with lower Aβ deposits (Mormino et al., 2014). Additionally, there was an interaction between APOE ε4 carrier status and Aβ, where ε4 carriers with high Aβ had the steepest decline over time in all measures of cognitive performance. This interaction suggests that these

factors synergistically impacted cognitive trajectories. Normally, it is difficult to parse the independent impact of Aβ and ε4 carrier status given they are highly correlated; however, the current findings suggest that these factors aren't redundant sources of information (Mormino et al., 2014). As discussed previously, the ε4 allele has implications in neuronal growth and integrity, so it is possible that this mechanism makes ε4 carriers especially susceptible to neuroanatomical insults, like the accumulation of Aβ. This further implies that APOE ε4 may impact cognitive outcomes via neuroanatomical pathways beyond amyloidosis, and instead could potentially impact cognition by heightening the neurotoxic effects of Aβ. This possibility could have been further explored had neurodegeneration been an additional neuroanatomical endpoint for this study, had the cognitive measures been more adept at probing subtle cognitive decline, and had the follow-up periods been longer.

These findings may also indicate a potential for ε4 carriership to impart an effect on cognition independent of the Aβ mechanism that may operate jointly to drive cognitive decline. This perspective was further explored in a longitudinal study with far longer follow-up. In a sample of 84 CN older adults with high Aβ deposition, cognitive endpoints were collected at baseline, 18-, 36-, and 54-month follow-ups (Lim et al., 2015). Cognitive performance was measured using the computerized Cogstate Brief Battery, MMSE, and the Clinical Dementia Rating scales. APOE ε4 carriers with high levels of Aβ showed significantly faster decline on memory tests than non-carriers (Lim et al., 2015). There was also a decline in attention and psychomotor function, however this decline did not reach significance. Over this 54-month period, non-carriers with high levels of Aβ experienced a nearly negligible level of decline in memory and no decline in

attention or psychomotor function. However, the relation between Aβ and cognitive performance was moderated by ε4 carrier status. The fact that ε4 carriership exacerbated the impact of preclinical Aβ on the domain of memory signifies that an additional neuroanatomical mechanism may be operative. This underscores the impact ε4 has on cognitive trajectories within preclinical samples and adds to the collection of studies previously discussed in this review that propose a potential neurodegenerative mechanism outside of amyloidosis that at least partially explains the impact ε4 has on cognition (Brookmeyer et al., 2018; Da et al., 2014). The current proposed study explored this potential mechanism by examining the effect ε4 carriership has on an AD-specific atrophy pattern indexed by SPARE-AD and whether this index mediates the relation of ε4 status to memory function and semantic fluency.

When considered as a whole, the literature pertaining to the APOE ε4 allele's impact on cognitive performance is still in need of further examination. It appears possible that in AD-susceptible domains, the mechanism through which ε4 impacts cognition occurs is via AD-specific neuroanatomical changes. To date, this paradigm has focused almost solely on the role of the APOE ε4 allele in amyloidosis, yet this mechanism holds little impact on preclinical cognition given that neuroimaging of Aβ is not closely tied to cognitive outcomes in this phase of AD (Chandra et al., 2019; Jack et al., 2018). Meanwhile, AD-specific brain atrophy is closely tied to the cognitive domains most impacted by AD-pathophysiology (mainly memory and semantic fluency), and this neurodegeneration can occur early within the cognitive continuum—even preceding amyloidosis (Brookmeyer et al., 2018). Thus, it remains critical to understand the relation of the APOE ε4 allele to AD-specific neurodegenerative profiles in the preclinical state,

and whether these brain correlates mediate the relation of the ε4 allele to cognitive function, specifically within the realms of memory and semantic fluency. This pathway may be explored with greater accuracy if using a neuroanatomical measure that is known to predict cognitive trajectories even among individuals with normal levels of amyloid, such as SPARE-AD (Da et al., 2014). This proposed study was the first to explore this mediational pathway. Importantly, this mechanistic pathway may not impact all populations equally, as it appears that the influence of the ε4 allele is not universal across all ethno-racial groups (Babulal et al., 2019). As discussed below, the notion that the strongest genetic predictor of AD risk (i.e., ε4) and cognitive decline may vary in impact based on race and ethnicity ultimately has a significant bearing on the framework of AD-specific health disparities research.

Rationale for Race as a Moderator

A key issue to highlight is that race itself is not a biological variable, but a social construct used to encompass the unique experience of a certain demographic. Due to a variety of historical and institutional factors influencing society, African Americans have endured—and continue to endure—distinct hardships that contrast the experience of their White counterparts. Studying race provides a proxy for the amalgam of unique experiences of a group that ultimately contribute to health and cognitive outcomes (Dimsdale, 2008; Graff-Radford et al., 2016; Profant & Dimsdale, 1999; Shonkoff et al., 2009; Tomfohr et al., 2016). Health disparities within the realm of cognitive performance may be due to multiple systemic factors such as: lack of resources, cultural differences, chronic exposure to harmful stimuli, assessment bias, and discrimination. One proposed pathway for this outcome is that historically disenfranchised racial groups experience

increased discrimination which leads to anger and emotion dysregulation, disrupted sleep quality, and ultimately an elevated and prolonged physiological stress response (Tomfohr et al., 2016). The consequence of a prolonged physiological stress response impacts the immune system, exacerbates CVD risk factors, and results in a deficit of the physiological mechanisms that typically buffer against cognitive decline (Dimsdale, 2008; Profant & Dimsdale, 1999; Shonkoff et al., 2009; Tomfohr et al., 2016).

It is further suggested that differences in the literature on cognitive performance and impairment between African Americans and White counterparts may be partially influenced by systemic barriers surrounding socioeconomic opportunities and the differences in quality of education and literacy among African Americans compared to Whites (Avila et al., 2021; K. Mehta et al., 2010; Sachs-Ericsson & Blazer, 2005; Weuve et al., 2018; Yaffe et al., 2013). These factors also influence the likelihood of cardiometabolic risk factors which not only impact African Americans at a higher rate but, may precipitate AD, VaD, and mixed dementia etiologies (Elahi & Miller, 2017; Love & Miners, 2016; Manly & Mayeux, 2004; Mehta et al., 2010; Sloan & Wang, 2005; Steenland et al., 2014). With all these factors, it is often overlooked that both AD and CVD disproportionately impact marginalized communities (Gilsanz et al., 2019; Glymour & Manly, 2008; Howell et al., 2017). Despite the impact of these factors on outcomes in African Americans, they do not fully explain the differences within the literature pertaining to racial differences in AD risk or cognitive decline. Attempting to understand the interplay between belonging to a disenfranchised identity and AD-specific outcomes throughout the cognitive continuum is a growing field for future research in primary prevention and for lessening health disparities.

Preclinical literature focused on health disparities within AD and associated cognitive function and decline are especially important given that AD prevalence is nearly two-fold for African Americans and incidence is 50-60% higher than their White counterparts (Power et al., 2020). This gives a particular urgency to understanding the factors that predict cognitive decline among African Americans and the factors driving these trajectories across the cognitive continuum, especially regarding conversion from normal cognition to MCI and AD. By probing the relationship between established predictors of AD-related cognitive decline and race, it is possible to better understand the pathways responsible for differences in African Americans' AD risk and trajectories. Key factors that warrant further exploration from a health disparities perspective are the genetic and neuroanatomical risk factors that may interact with race in influencing cognitive performance.

Race and APOE

As discussed previously in this review (see *Genetic Underpinnings*), APOE ε4 carrier status is the most influential non-causative genetic risk factor for the development of AD-pathophysiology; however, when examining the prevalence of this allele across racial-ethnic groups, it has been observed that African Americans have a 1.4 times higher likelihood of carrier status than Whites (Logue et al., 2011; Rajan et al., 2019; Weuve et al., 2018). Additionally, African Americans exhibit higher incidence and prevalence of AD than Whites (Chin et al., 2011). Following this logic, it could be assumed then that the higher proportion of ε4 alleles in the African American population may be partially responsible for the higher incidence and prevalence of AD in this population. However, the literature regarding ε4 status in African American populations does not seem to

reflect such a direct relation between ε4 carrier status and AD (Evans et al., 2003; Maestre et al., 1995; Mayeux et al., 1993; Rajabli et al., 2018; Tang et al., 1996; Weuve et al., 2018).

In fact, in 1995, a preliminary study investigating the relation between APOE ε4 and AD risk among Whites, African Americans, and Caribbean Hispanics found a strong association in Whites, a lack of association in African Americans, and an intermediate association for the Hispanic group (Mayeux et al., 1993). This finding marked the beginning of examining racial differences among APOE status and AD risk associations. The authors of this preliminary study conducted a follow-up in a community-based sample of 145 patients with AD (41 African American, 61 Hispanic, 43 White) and 206 healthy older adults (57 African American, 90 Hispanic, 59 White; Maestre et al., 1995). Here, the association between ε4 status (both homozygous and heterozygous) and AD was seen across all racial/ethnic groups; however, in heterozygous ε4 carriers the association was weakest among African Americans despite having higher frequencies of the allele than other races (Maestre et al., 1995). This finding was replicated by Tang et al. (1996), who similarly found a significant association of homozygous ε4 status and AD across all racial/ethnic groups, but a weaker association with heterozygous ε4 status among African Americans (Tang et al., 1996). Overall, these early studies set the stage for trying to understand the interaction between ε4 status and race with respect to AD and its risk factors, particularly among African Americans.

To help answer this question, a meta-analysis comprised of studies from 40 research teams that spanned a variety of countries, calculated the association of the ε4 allele and AD by race. These studies were taken from community and clinical samples

and brain banks and had a total of 5930 patients who met criteria for probable or definite AD and 8607 controls without dementia; however only 235 of the patients and 240 of the controls were African American, while the vast majority were White. In this meta-analysis it was once again found that the ε4 allele was only weakly associated with AD risk among African Americans, but strongly associated in Whites (Farrer et al., 1997). It is important to note that although the associations were weak among African Americans, they were still present. This suggests that the ε4 allele is still a detrimental variant for African Americans in terms of AD-pathophysiology, just to a lesser extent than in Whites. However, one potential explanation for this attenuated association may relate to methodological weaknesses from prior research, particularly the scarcity of African American subjects. This strongly suggests that the field must shift away from using predominately White samples.

To this end, a community-based study of 56 Nigerians and 85 African Americans aged 65+ evaluated the association of the ε4 allele with AD; results revealed a highly significant association within the African American sample but no association in the Nigerian sample despite having higher frequencies of the ε4 allele (Gureje et al., 2006; Osuntokun et al., 1995). This design was later replicated with additional enrichment cohorts, a larger number of participants with incident AD, extended analyses to test for APOE ε4-cognitive decline associations in both cohorts, and longer follow-up. The results indicated that, among African Americans, there was a significant relationship between ε4 carrier status and AD risk regardless of whether homozygous or heterozygous; however, only being homozygous for the ε4 allele conferred associations in the Nigerian sample, and even then the relation was weak (Hendrie et al., 2014). This

finding was surprising given that the prevalence of carrier status was higher in the African group than the African American group. This may suggest that stressors and other environmental or lifestyle exposures encountered by African Americans may, in part, explain this difference in the ε4-AD association when compared to African cohorts; however, an alternative explanation could lie in the genetic variability between these two groups, as most African American samples have an admixture of African and European ancestry. This raises the question of whether African ancestry potentially lowers the impact of the ε4 allele on AD risk, and that perhaps the admixture of African and White ancestry in African Americans leads to an increased association of ε4 with AD risk.

This question was investigated in a study looking at the ancestral origin of the ε4 allele in African American and Puerto Rican populations, which ultimately found that ε4 alleles on an African-ancestral region conferred a lower risk for AD than among those with a European ancestral allele, regardless of being either Puerto Rican or African American (Rajabli et al., 2018). This suggests that inheritance of an APOE ε4 allele deriving from African ancestry may be more protective against AD risk than those inherited from European ancestry. Furthermore, within the African American sample, those that had an ε4 allele from European ancestry had a higher AD risk than those that had the allele from African ancestry (Rajabli et al., 2018).

Interestingly, in one of the earliest investigations exploring ε4-AD associations, it was hypothesized that one of the mechanisms through which African Americans experience a weaker association may be due to modifier genes on the locus shared with ε4 (Maestre et al., 1995). Decades later, it seems they may be at least partially correct, and that ancestral inheritance of this gene is involved in this process. This may give

further credence to the notion that the inconsistencies and weak associations regarding ε4 and race may be due to heterogenous ancestral genetic profiles among the African American samples studied. This is a consequence of relying on self-reported race instead of an analysis of the admixture of different ancestries among these samples.

Interestingly, if pushed forward, this finding could shift the current conceptualization of race and how it is measured in studies integrating genetic data; in fact, it has been suggested previously that self-reported race is an inadequate marker for genetic differences and may lead to harmful generalizations from health disparities research (Shields et al. 2005). This work in particular suggests that in the context of ε4 carrier status, a more African ancestry may be protective against AD while a more European ancestry may be a risk factor. This also emphasizes the notion that due to unique genetic profiles; ancestral race could be a variable that modifies the relation between ε4 and AD risk— possibly even independent of socioeconomic stressors or other lifestyle factors encountered by African Americans. As the present study did not have genetic data pertaining to the ancestral origin of the ε4 allele, it was assumed that African Americans had a higher likelihood of ε4 inherited from African ancestry compared to Whites, and thus as a whole would have an attenuated (yet still present) ε4-AD association.

The differential impact of ε4 status on AD risk based on race directly translates to its relation to cognitive performance (Babulal et al., 2019; Elias-Sonnenschein et al., 2011; Ren et al., 2020; Varatharajah et al., 2019). Although it has been discussed previously in this review that ε4 carrier status has been implicated in poorer cognitive trajectories, these associations—much like the associations with AD risk—are weaker

among African American samples than Whites (Blair et al., 2005; Borenstein et al., 2006). One study examined the association of ε4 carriership and cognitive function in 253 non-demented African Americans and 466 Whites ranging from 60–84 years old gathered from two community-based samples (the Hillsborough Elder African-American Life Study/HEALS and Charlotte County Healthy Aging Study/CCHAS respectively; Borenstein et al., 2006). In this study, five cognitive measures were used: an abbreviated Mini-Mental State Examination (3MS) and four measures derived from the modified Hopkins Verbal Learning Test (HVLT). This resulted in gauging the ε4-cognitive performance association in global cognitive status and a test of the memory domain, which were dichotomized into low performance (lowest 20th percentile) and high performance. White participants with an ε4 allele were 3.42 times more likely to perform poorly on recognition discrimination than those that were not carriers, while no ε4-cognition associations were noted in African Americans (Borenstein et al., 2006). A limitation to note is that although the African American participants had a higher frequency of the ε4 allele, only 12 were homozygous carriers, whereas heterozygous African American carriers show the weakest relation with AD risk. Additionally, the use of an older sample in this study may have led to the accumulation of prodromal AD-pathology in participants that went unnoticed (Borenstein et al., 2006). As there does seems to be an overall association between ε4 carrier status and AD risk among African Americans in some of the literature—albeit weaker than Whites—the relation should translate to ε4 carrier status and cognition relations. The finding from Borenstein and colleagues (2006) seems to contradict this rationale; however, as noted previously (see *APOE and Preclinical Cognitive Outcomes*) a lack of ε4-cognition relations often stems

from methodological pitfalls (O'Donoghue et al., 2018; Wisdom et al., 2011). This holds especially true within the study of ε4-cognition relations among African Americans.

It has been argued that those studies that do not identify racial differences when examining genetic factors in cognitive performance or decline in African Americans are due in great part to the methodology of the studies (Fillenbaum et al., 2001; Sawyer et al., 2009). In a more methodologically sound examination of over 2,076 participants spanning a 10-year period and multilevel models for repeated measures, it was found that the APOE ε4 allele predicted cognitive decline for both African Americans and Whites (Sawyer et al., 2009). The presence of at least one ε4 allele predicted more cognitive errors across items of the Short Portable Mental Status Questionnaire (SPMSQ) at wave 1 and a faster rate of longitudinal decline irrespective of race. However, regardless of ε4 carrier status, African Americans experienced a faster rate of cognitive decline than Whites (Sawyer et al., 2009). This was the first study to note APOE ε4 impact on cognitive decline in both Whites and African Americans (Sawyer et al., 2009). The authors argue that four major methodological factors contributed to their positive finding. These methodological limitations, which pertain to the overall literature, are discussed further below.

The first methodological pitfall of many investigations is inadequate sample size, particularly of African American participants. This has a significant impact on the statistical power of studies pursuing the examination of racial differences in ε4-cognition relations. Particularly those that did not find significant relations between ε4-cognition typically had few African American participants (Sawyer et al., 2009; Weuve et al., 2018). The second pitfall centers on the use of dichotomous outcome measures, instead

of continuous cognitive measures that would improve the likelihood of observing a true ε4-cognition relation. The use of dichotomous classification of outcomes using global screening measures of impairment offers a quick and convenient strategy for estimating overall cognitive status yet is an especially weak method given that more robust neuropsychological tests are available to measure a variety of specific domains of function that are affected by AD pathophysiology. For example, the domains of memory and semantic fluency are often targeted first within the AD-pathophysiological process and early manifestations of decline in these domains are easily measured with continuous measures (i.e., CVLT and Semantic Fluency). Additionally, the reliance on screening measures ties to a third methodological weakness regarding measurement bias, as false-positive rates for dementia on standardized screening tests are typically higher for African Americans than Whites (G. Fillenbaum et al., 1990; Sawyer et al., 2009). This places the onus on researchers to focus on more domain-specific measures of cognition and move away from a reliance on global screening measures. Lastly, it is argued that proper statistical adjustment methods are needed when studying the influence of race. This is essential because the concomitant impact of socioeconomic status and education/literacy may mask the predictive power of ε4 carriership on cognitive performance, and must be adjusted in these models (Sawyer et al., 2009; Weuve et al., 2018). Some authors posit that this could be why cross-sectional studies in solely African American samples typically find a significant relation between ε4 and AD risk, as between-group variability among these factors is reduced (Hendrie et al., 2014; Sawyer et al., 2009).

Overall, this suggests that the mixed findings regarding race-related differences in ε4-cognition in preclinical studies may be due to methodological limitations and weaknesses in probing this relation. As of the writing of this document, the general consensus in the field views the association between ε4 and cognition in African Americans as being mixed or inconsistent and warranting further study (Alzheimer's Association, 2021). This further highlights the need for new studies to be produced that seek to address these limitations and incorporate improved methodologies in more diverse and representative samples in order to expand the investigation of race effects on ε4-cognition relation. The proposed study aimed to address and build upon the suggestions made by Sawyer and colleagues (2009) by ensuring a larger sample size than most prior studies that have contrasted African American and White participants; a higher percentage of African American participants; the use of AD-specific continuous measures of cognition; and suggested statistical adjustment variables.

A related issue is that most studies probing preclinical ε4-cognition associations among African Americans relied on adults over the age of 65. As discussed previously, (see *APOE and Preclinical Cognitive Outcomes*) reliance on older adult preclinical samples likely confounds the ε4-cognition association due to subtle impacts of accumulating AD-pathology, meaning that studies using older samples may not be truly preclinical due to unaccounted and insidious AD processes (O'Donoghue et al., 2018; Wisdom et al., 2011). Additionally, older samples may also experience higher rates of vascular pathology which may mask the relation between ε4 and cognitive performance in preclinical samples (Iadecola, 2013). In addition, racial disparities in mortality rates may disproportionately lead to selection bias with African Americans in these older adult

cohorts. This is because African Americans from the 65+ birth cohort of past studies had a lower likelihood of reaching the age of 65 than Whites; those that did reach this age may have had specific traits that not only improved survival but also conferred cognitive benefits (Weuve et al., 2018). To address this, the proposed study had a primarily middle-aged preclinical sample. Application of these methodological considerations in the present study may help further clarify the literature regarding ε4-cognition associations in African Americans compared to Whites.

Race and Brain Outcomes

As discussed previously, AD-specific neurodegenerative profiles correlate strongly with AD-pathology, neuropsychological performance in AD-specific domains, and progression along the cognitive continuum towards dementia (Sencakova et al., 2001; Talwar et al., 2021; Vemuri & Jack, 2010; Wang et al., 2015). However, most research studies probing ε4-brain correlates and brain-cognition correlates, have been performed in predominately White samples (Babulal et al., 2019; Sencakova et al., 2001). This is problematic because, as detailed above, there is a need to further probe race-ε4 relations and address whether the inconsistencies between e4-cognition associations in African Americans are due to solely methodological limitations of prior literature or if there may be differences in neurobiological processes or AD-pathology between African American and White subjects. As of now racial differences regarding e4-brain and cognition correlates are extremely understudied and need further examination (Babulal et al., 2019).

To examine AD-specific neurodegenerative profiles among an African American sample, a cross-sectional study of 54 healthy African American subjects and 32 African

Americans with AD was implemented (Sencakova et al., 2001). Serial hippocampus volumetric measures were derived from three-dimensional MRI scans for both groups and compared (Sencakova et al., 2001). Additionally, a set of neuropsychological tests assessing global cognition and the domain of memory were conducted. The global cognition measures were the Mattis Dementia Rating Scale and the MMSE, while the domain of memory was measured via a list-learning procedure (Auditory Verbal Learning Test), paragraph recall (Wechsler Memory Scale–Revised: Logical Memory), and nonverbal memory measures (Wechsler Memory Scale–Revised: Visual Reproductions) (Sencakova et al., 2001). These measures were modestly correlated with hippocampal volumes of the AD patients, but not the healthy participants. It was found that hippocampal atrophy was a major indicator of AD pathology for African Americans within this study (Sencakova et al., 2001). Additionally, the ε4 allele was found at a higher rate in those within the AD group.

It has been well established that a lower hippocampal volume, particularly in the context of the ε4 allele, in AD patients is a typical neurodegenerative pattern found in Whites as well (Jack et al., 2018; Schuff et al., 2008; Sencakova et al., 2001; Vemuri & Jack, 2010; Wang et al., 2015). Thus, the findings of Sencakova and colleagues (2001) gives credence to the suggestion that the brain-correlates in African Americans, much like the cognitive-correlates observed throughout the cognitive continuum, match the directionality observed in Whites. However, just as there are discrepancies in the ε4-cognition literature among African Americans, so too are there similar discrepancies regarding AD-specific neuropathologic differences between African American and White individuals (Graff-Radford et al., 2016; Wilkins et al., 2006). As such, it is possible that

measures of neurodegeneration may reveal differential insight with respect to race differences in ε4-brain relation (see *AD-Specific Brain Correlates*). To this end, a cross-sectional study recruited similar numbers of cognitively normal, MCI, and AD individuals to a total of 135 older adults (65 African American and 70 White), with the aim to examine racial differences of AD biomarkers between African Americans and Whites across AD states (Howell et al., 2017). In this sample, African Americans and Whites had similar age, sex, education, proportion with ε4 allele, and vascular risk factors (except hypertension and diabetes, which were higher in African Americans), thus these factors were adjusted in the statistical models.

Cognitive performance was measured across four domains: memory (indexed by the Consortium to Establish A Registry for Alzheimer's Disease word list delayed recall and the Brief Visual Memory Test–Revised delayed recall), language (measured by the Boston Naming Test and category fluency), visuospatial function (determined by the Judgment of Line Orientation and Rey-Osterrieth complex figure test) and executive function (indexed by Trail Making Test B, reverse digit span, Symbol Digit Substitution Test, and letter-guided fluency; Howell et al., 2017). Z-scores were calculated for each domain by averaging subtest Z-scores, and the domain-specific Z-scores were further averaged to generate a composite cognitive Z-score (Howell et al., 2017). When assessing biofluid and neuroimaging differences among African Americans and Whites, it was determined that cognitively normal and MCI participants of both groups had comparable $A\beta_{42}$, white matter hyperintensities (WMH) , and hippocampal volumes when adjusting for age, sex, education, proportion with ε4 allele, and vascular risk factors. WMH reflect lesions that are highly associated with brain atrophy patterns and

are a marker of brain microvascular disease that have been associated with vAD, AD, as well as cognitive decline (Love & Miners, 2016; Rizzi et al., 2014; Stampfer, 2006). This prompted a linear regression analysis probing whether race moderated the impact of WMH on cognition. This was done in a stepwise fashion, wherein each independent variable (age, education, Aβ42, t-tau, WMH, race, sex, ε4 carriership, ABCA7 risk carriership, hypertension, and diabetes) generated a model of main effects, and the interaction term was added to the model afterward. At the univariate level, cognition was influenced by ε4 for both races. However, the interaction term demonstrated that the same level of lesion volume was associated with a significantly lower mean cognitive score within African Americans than Whites - the same degree of WMH had a greater impact on cognition in African Americans than Whites (Howell et al., 2017). Because those with non-AD dementias or suspected non-AD impairments were excluded from this study, it was suggested that these findings could not be explained by the pathology of another dementia type; however more detailed neuropathologic characterization may be necessary to ensure subtle vascular pathology or other non-AD processes were not involved. The findings suggest that the impact of neuroanatomical insults on cognition may be more pronounced in African Americans, but independent of APOE ε4.

A more recent cross-sectional study aimed to examine racial differences in molecular and neuroimaging AD biomarkers within a sample of 1255 community-dwelling participants (173 African American and 1082 White; Morris et al., 2019). This sample was composed of cognitively normal participants and symptomatic AD patients, where semi-structured clinical interviews and neurological examinations determined clinical status (i.e., whether a participant was CN or had dementia) via the Clinical

Dementia Rating (Morris et al., 2019). Of the 173 African American participants, 67.1% were considered CN while of the 1082 Whites, 66.9% were CN. In this study, all analyses first examined the interactive relations between race and each of the other covariates with respect to the biomarkers, and in the absence of an interaction, then the race main effect on the biomarkers was reported (Morris et al., 2019). In terms of neuroimaging findings, no significant interactions were found and there were no racial differences in the frequency of cerebral ischemic lesions or Aβ accumulation in amyloid PET when adjusting for sex, ε4 carrier status, age, educational level, clinical status (CN or dementia), and body mass index. Racial difference in total hippocampal volume was also analyzed using the same adjustment variables. It was found that African American participants had smaller mean total hippocampal volumes than White participants; however, this was only for participants with a family history of dementia. (Morris et al., 2019) Those without a family history of dementia, had no racial differences in hippocampal volume.

Regarding biofluid data, CSF concentrations of $A\beta_{42}$ were comparable among African American and White participants; however, there were racial differences in terms of mean CSF concentrations of phosphorylated tau (p-tau_{181}) and total tau. When adjusting for ε4 carriership, sex, educational level, Clinical Dementia Rating, body mass index, and family history of AD; the mean concentration of p-tau_{181} and total tau was lower in African Americans than Whites in this study (Morris et al., 2019). Race * ε4 carriership interactions were examined for p-tau_{181} and total tau, where it was determined that African American carriers of the ε4 allele had significantly lower concentrations of both biomarkers in their CSF than Whites. However, African American non-carriers of ε4

did not differ from Whites in terms of p-tau$_{181}$ and total tau concentration in the CSF. As a whole, this may suggest the presence of racial differences in the AD-pathophysiological process, where the impact of the ε4 allele on African Americans may result in lower CSF biomarker concentrations. This mirrors the weaker ε4-AD risk association in African Americans. Furthermore, this study further suggests that African Americans may be more vulnerable to the risk factors that exacerbate neurodegeneration, exhibited by smaller hippocampal volume in those with a familial history of dementia.

Results of this study may suggest that the relation between race and brain biomarkers of AD risk are such that African Americans are more likely to be impacted by certain aspects of the AD-pathophysiologic process. As mentioned previously in this review, excessive Aβ deposition is thought to be responsible for the formation of amyloid plaques, and partially involved in the formation of neurofibrillary tangles, which is closely tied with the APOE ε4 allele and tau-based mechanism (Elahi & Miller, 2017; Masters et al., 2015; Tanzi, 2012). This was expanded upon in a multi-ethnic sample of 116 dementia-free participants, where a race-stratified longitudinal analysis of amyloid-beta deposition in the brain and its relation to cognitive outcomes was conducted (Gu et al., 2015). The amount of Aβ deposition was calculated for four pre-established ROIs (frontal cortex, temporal cortex, parietal cortex, and cingulate gyrus), as well as for the amount of Aβ deposition found globally throughout the brain. The sample consisted of older adults, with approximately 46% African Americans in the sample, and cognition was measured across several domains using continuous measures of cognitive performance. Memory was assessed with the total recall, delayed recall, and delayed recognition components of the Selective Reminding Test and the recognition component

from the Benton Visual Retention Test (Gu et al., 2015). The language domain included measures of naming, letter fluency, category fluency, verbal abstract reasoning, and repetition and comprehension. Executive function was assessed with the Color Trails test, while visuospatial ability was assessed with the Rosen Drawing Test, the BVRT–Matching, and the Identities and Oddities subtest of the Mattis Dementia Rating Scale (Gu et al., 2015). This was done in a manner that encompasses domains specific to AD (such as memory and semantic fluency), as well as other domains that were broadly associated with dementia and cognitive decline but not particularly indicative of preclinical AD (such as visuospatial ability or executive function). A composite score that was determined by the mean of the four prior domains was then calculated.

As expected from previous literature, Aβ was not associated with cognition cross-sectionally; however, longitudinally it was found that a higher level of global Aβ burden or Aβ in each ROI was associated with a steeper decline annually on the mean cognition score, executive function, and language tests in African Americans but not Whites (Gu et al., 2015). Likewise, for those that were ε4 carriers, higher levels of global Aβ or Aβ in each ROI were also associated with a steeper decline annually on the mean cognition score, executive function, language tests, and an even faster memory decline than non-carriers. With regard to Aβ deposition within the ROIs, there were significant associations between decline in the domain of executive function and Aβ deposition in the temporal and frontal region among cognitively normal subjects (Gu et al., 2015).

This study not only showcases the differential impact of Aβ on cognition over time between Whites and African Americans, but also highlights the relation between changes in specific brain regions and cognitive performance. It additionally reinforces the

impact that the ε4 allele has on cognitive decline across race. Although ε4-Aβ and race-Aβ associations on cognitive decline were observed in this study, they were done so separately and the potential moderation of race on ε4-brain endpoints was not explored. Results of this study suggest that race may moderate the relation of brain outcomes on cognitive function and reinforces the need to build upon the current literature by further examining potential race and ε4 carriership interactions in these relations.

In probing the question of how race and the ε4 allele interact to impact neuroanatomical profiles, a longitudinal study of 329 dementia-free older adults was conducted (Gottesman et al., 2016). Of the sample, nearly 41% were African American and race * APOE interactions on Aβ were probed. This study found that African Americans had a two-fold increase in rate in global Aβ deposition than Whites and this pattern remained even when adjusting the model for hypertension, diabetes, MCI defined by the classification within the ARIC protocol, WMH, and total intracranial volume (Gottesman et al., 2016). This suggests that the racial disparities in neuroanatomical endpoints, at least in the present study, were not primarily mediated by vascular risk factors. However, there was no evidence for a race * APOE interaction on Aβ in the brain (Gottesman et al., 2016).

As mentioned previously in this review (see *APOE and Preclinical Cognitive Outcomes*), the current conceptual framework primarily relies on the APOE ε4 allele's role in amyloidosis, despite neurodegeneration profiles being highly predictive of cognitive outcomes and potentially acting as a mediator for the ε4-cognition relation. This leaves much to be elucidated regarding atrophy pattern measures and the ε4-cognition association, especially in terms of racial differences. The rationale for this

perspective is due to the direct impact APOE ε4 allele has on the neuronal growth, brain outcomes, lipid metabolism, and how these processes may vary depending on race (de la Torre, 2018; De Reuck et al., 2018; Mahley, 1988; Masters et al., 2015; Tanzi, 2012; Wei et al., 2017). This explicit focus on race is important because AD clinical and preclinical cohorts are predominately White and leave African Americans underrepresented in the literature, which ultimately exacerbates the gap in knowledge pertaining to AD-specific brain-correlates in African Americans (Morris et al., 2019). As neurodegeneration is the most predictive neuroimaging marker for cognitive outcomes, a focus on this measure is germane to understanding a relatively understudied potential mechanism in which ε4 impacts cognition via neurodegeneration and atrophy.

Furthermore, race moderation remains to be studied using a robust machine-learning derived neuroimaging biomarker. In fact, the present study was the first to probe a SPARE-AD * race interaction on cognitive performance. The importance of this pathway is that it would elucidate information regarding AD-specific atrophy patterns and how these patterns may impact cognition depending on race. Prior literature has suggested that African Americans may be more susceptible than Whites to the cognitive decrements imparted by neuroanatomical insults (Gottesman et al., 2016; Gu et al., 2015; Howell et al., 2017). This would indicate that in the proposed study, the interaction between race and SPARE-AD index on cognition may actually be accentuated in African Americans when compared to Whites, as it is a pathway that does not rely on ε4 effects. This could ultimately provide an explanation for why AD risk and cognitive decline occurs at a higher rate within African Americans, despite having a seemingly attenuated ε4-AD risk relation. In implementing race as a moderator for this mediational pathway, it

is also imperative to properly adjust the model for potential confounders to maximize the true effect of any potential interactions or main effects. These approaches are worthwhile because they further positioned the current study to expand upon the scarce literature regarding racial differences in ε4-cognition associations within a middle-aged preclinical sample and elucidate novel mediational contributions of a unique neuroimaging biomarker.

Rationale for Covariates

Age

Age is the primary risk factor for AD (Alzheimer's Association, 2019; Sheppard & Coleman, 2020). It was originally estimated that AD prevalence doubles every five years after the age of 60; however, we see the percentage of people suffering from AD going from 3 percent in the 65-74 age group to 17 percent for the 75-84 age group, to 32 percent at age 85 and older (Alzheimer's Association, 2019; Hebert et al., 2013). In healthy older adults, it has been found that with increasing age there is significant annual volume loss in total, grey, and white matter (Resnick et al., 2003). Age related volume loss and atrophy, particularly in the hippocampal regions, have long been associated with cognitive decline and instances of poor cognitive performance (Stark & Stark, 2017). Even in instances where atrophy is not present, age is associated with decreased activity in resting-state functional connectivity, attention networks, and hippocampal connectivity (Panitz et al., 2021). This impact on cognition and neuroanatomical endpoints motivates the rationale for adjusting all analyses by age.

Literacy

Fewer years of education and poor education quality are often common in African Americans within health disparities research, and these factors may impact cognitive decline and AD risk (Sachs-Ericsson, 2005; Sawyer et al., 2009). However, years of education has been shown to be a poor reflection of the value of educational experience and native ability among ethno-racial groups, while literacy level may be more strongly associated with the quality of education in diverse cohorts (Babulal et al., 2019; Dotson et al., 2009; J. J. Manly et al., 2003, 2005). Most of the literature examining the association between literacy and cognitive function have documented that higher levels of literacy reflect better performance on select neuropsychological tests, particularly verbal and non-verbal memory, attention, orientation, and visuospatial ability (Dotson et al., 2009; J. J. Manly et al., 2003, 2005; Reis et al., 2003). This association is not limited to cross-sectional examinations, but has been seen in longitudinal studies as well, with lower levels of literacy precipitating faster rates of cognitive decline (Manly et al., 2003, 2005). The impact of these factors may mask the predictive effect of the APOE ε4 genotype by generally increasing the incidence of diagnosed AD in the African American population (Sawyer et al., 2009). As such, literacy was included as a covariate in all analyses. Literacy has also been known to impact

Poverty Status

Another factor that may impact the predictive effect of APOE ε4 genotype on cognition within African Americans is socioeconomic status indexed by poverty or other income based measures (Sawyer et al., 2009). Lower socioeconomic status, as indexed by poverty status or other income based measures, has long been associated with poor

cognitive outcomes, particularly in the domains of memory, language, visuospatial ability, and executive function (Babulal et al., 2019; S. C. Levine et al., 2005; Singhmanoux et al., 2005). Additionally, low income, assets, and other means of socioeconomic status have been associated with lower baseline cognitive scores and more marked decline in cognition over time (Koster et al., 2005; Mehta et al., 2004). Furthermore, the use of poverty status is a more accurate and reliable measure of socioeconomic status than self-reported income. The mechanisms behind the association of SES and cognitive performance are unclear, though mounting evidence suggests that poverty impacts neuroanatomical endpoints and thus leads to poorer cognitive performance (Brito & Noble, 2014; Staff et al., 2012; Turrell et al., 2002). In particular, low socioeconomic status has been associated with lower brain volumes and increased atrophy (Fotenos et al., 2008; Raz et al., 2005; Staff et al., 2012). These associations give credence to adjusting for poverty status in all analyses of the present study.

Sex

In terms of impact on cognitive performance, the literature suggests that women perform better in tests of perceptual and psychomotor speed, list learning, and verbal ability while men display better spatial ability; however these differences exhibit small effect sizes (Hyde, 2016; Lezak et al., 2012). Additionally, although it has been suggested that brain regions dealing in memory and cognitive performance (particularly the hippocampus) are larger in men than women, a recent meta-analysis has demonstrated that when adjusting for intracranial and total brain volume this difference disappears (Tan et al., 2016). Of interest is the sex disparity in AD, where over 60% of individuals with the disease are women (Riedel et al., 2016). This could be due to a difference in

mortality, wherein the ε4 allele was associated with shorter survival in men but not in women (Dal Forno et al., 2002). Additionally it has been suggested that the ε4 allele drives a faster decline in mental status for women, while driving a faster decline in memory for men (Makkar et al., 2020). Because of this sex was controlled in all analyses.

Statement of the Problem

The Proposed Study

Dementia is a growing public health crisis with the latest report from the CDC demonstrating 271,872 U.S. deaths in 2019, with 121,499 (45.69%) of those attributed to AD (Alzheimer's Association, 2021; Centers for Disease Control and Prevention, 2019). In terms of the most up to date prevalence estimates, nearly 6.1 million individuals living in the United States had AD in 2020 and that number is expected to grow to 6.2 million in 2021 as the "baby boomer" generation continues to age (Alzheimer's Association, 2021; Rajan et al., 2021). Thus, the importance of elucidating key mechanisms of the early AD-pathophysiological process during the preclinical state is imperative in order to develop prevention and intervention measures to alter the AD-pathophysiological continuum. In that regard, because AD-pathophysiology typically follows a predictable pattern of neuroanatomical change and cognitive decline, it is imperative to assess measures that are most sensitive to observing the associated brain and cognitive correlates (Braak & Braak, 1991; Jack et al., 2018; McKhann et al., 2011). The use of machine learning methodologies has elucidated several powerful neuroimaging biomarkers, such as the SPARE-AD index (Davatzikos et al., 2009; Fan et al., 2008; Kumar et al., 2021; Lin et al., 2021) that indicate a multivariate pattern of brain atrophy associated with AD and risk for progression through the AD continuum. To our

knowledge, no prior studies to date have addressed whether this measure of AD-specific neurodegeneration mediates the relation of APOE ε4 alleles to cognitive function either at all, or specifically in a preclinical sample. However, the relations of APOE ε4 to both AD-specific neurodegeneration and cognitive function varies by race, with some studies suggesting a weaker association among African Americans than Whites (Alzheimer's Association, 2021; Borenstein et al., 2006; Maestre et al., 1995; Mayeux et al., 1993; Sawyer et al., 2009; Tang, 1998; Weuve et al., 2018). Currently, there is a scarcity of studies probing ε4-cognition, and almost none examining ε4-brain atrophy relationships among African American and White preclinical samples, and those that have been published suffer from methodological issues that limit their findings. Thus, the proposed study probed and expanded on the APOE ε4 research regarding differential impact among African Americans and Whites in the following ways: evaluated a novel mediational pathway utilizing a sensitive and specific neuroimaging biomarker of neurodegeneration (i.e. SPARE-AD), used a primarily middle-aged preclinical sample of African American and White participants, had a high percentage of African American participants, used sensitive cognitive measures derived from a neuropsychological battery instead of simple dichotomous measures, properly adjusted for potentially confounding variables (i.e. age, quality of education indexed by literacy, socioeconomic status indexed by poverty status, and sex), and had a sample size sufficiently powered to detect a medium effect size.

Specific Aims

The present study examined whether the association of APOE ε4 status and AD-associated cognitive outcomes is mediated by MRI-assessed AD risk pattern of brain

atrophy (SPARE-AD) and if the entire model was moderated by race. This model was adjusted for poverty status, literacy, sex, and age in a sample of socioeconomically diverse urban-dwelling adults (Figure 1). The cognitive outcomes measured are the Semantic (Animal) Fluency test and the California Verbal Learning Test (total, short free recall, and long free recall). Significant interactive relations of race and APOE ε4 to the outcomes were expected as follows:

Hypotheses:

Based on these aims I hypothesized the following:

1. Race would moderate the relation of APOE ε4 status to cognitive function such that Whites with APOE ε4 would have the lower levels of performance on cognitive outcomes than Whites with non-APOE ε4 status. A similar, but less pronounced relation would be apparent among African Americans.
2. Race would moderate the relation of APOE ε4 status to SPARE-AD such that Whites with APOE ε4 would have higher levels of SPARE-AD than Whites with no APOE ε4 alleles. A similar, but less pronounced relation would be apparent among African Americans.
3. Race would moderate the relation of SPARE-AD score to cognitive function such that Whites with greater SPARE-AD would have lower levels of cognitive function than Whites with lower SPARE-AD. A similar, but potentially more pronounced relation may be apparent among African Americans.
4. The significant interactive relation of race and APOE to cognitive function would be mediated by SPARE-AD (i.e., moderated mediation)

Methods

Participants

Participants were drawn from the Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS) SCAN study, which is an ancillary study of the larger HANDLS investigation. HANDLS is a prospective, epidemiologic study aimed at understanding health disparities across a socioeconomically diverse group of African American and White adults, while the ancillary study is an investigation of brain health disparities attributable to race and socioeconomic status. The current participants were recruited from HANDLS to take part in HANDLS SCAN, which obtained MRI data from HANDLS participants that completed their first or second complete follow-up visit.

HANDLS study exclusions were 1) outside of the age range 30-64 years at baseline testing; 2) currently pregnant; 3) within six months of active cancer treatment (i.e., chemotherapy, radiation, or biological treatments); 4) unable to provide informed consent due to mental incapacity resulting from drug or alcohol intoxication, severe developmental disability, or dementia; 5) unable to complete at least five of the nine tests given on the Mobile Medical Research Vehicle (MRV; the dual energy X-ray absorptiometry, intimal medial thickness, pulse wave velocity, physical exam, medical history, ACASI questionnaire, neuropsychological tests, physical performance, and dietary recall); 6) without a verifiable address or valid government issued identification at time of consent; 7) had uncontrolled high blood pressure (>160/100).

HANDLS SCAN participants had the following additional exclusions: history of dementia, stroke, or transient ischemic attack; history of carotid endarterectomy; MRI contraindications (e.g., claustrophobia, indwelling ferromagnetic material); diagnosis of a

terminal illness (e.g., metastatic cancer, end-stage liver, or pulmonary diseases); or other neurological disorder (e.g., multiple sclerosis, Parkinson's disease).

Out of the 2468 actively enrolled HANDLS participants (at the time), 252 participants enrolled in HANDLS SCAN and successfully completed neuroimaging. Of these participants, 238 have usable neuroimaging data following exclusions for incidental clinical findings or motion artifact. Following exclusion for missing sociodemographic (poverty status, literacy, age, sex, race), genetic (ε4 status), or SPARE-AD data participants are 165 African American (AA) and White, urban dwelling adults were available for analysis. After further exclusions for missing cognitive tests, the available sample sizes were 158 with Semantic Fluency data, 143 with CVLT total score, 140 with CVLT short free recall score data, and 142 with CVLT long free recall score data. Thus, the proposed analyses utilized 158 participants in the Semantic Fluency analyses (mean age = 53.4, 35.4% African American, 57% Female, 31% below poverty status) and 140 participants across the CVLT analyses (mean age = 53, 37.9% African American, 55.7% Female, 34.3% below poverty status).

HANDLS Procedures

Participants were recruited from 13 Baltimore neighborhoods that were pre-determined to yield a diverse range of socioeconomic and demographic characteristics. HANDLS commissioned a federal contractor to identify eligible participants via interviews and invited one or two eligible individuals per household to participate in the study. Those that were recruited consented to complete a household survey inquiring about demographic, psychosocial, and physiological information. At the conclusion of this first visit, an appointment for a second visit on the HANDLS Mobile Medical

Research Vehicles (MRVs) was scheduled, with the MRVs parking in the participant's neighborhood. For the second visit, participants fasted the night before their appointment and avoided smoking and strenuous physical activity for at least 30 minutes prior to their visit on the MRVs. Participants then completed a dietary recall, medical history and comprehensive physical examination, and additional biomedical, psychological, neuropsychological, and physical performance assessments on the MRVs by trained personnel. HANDLS data collection is ongoing (Wave 5), and participants are reevaluated approximately every three to four years.

Eligible HANDLS participants were approached during their Wave 3 or 4 MRV visit and invited to participate in HANDLS SCAN. Those who were interested in volunteering for this ancillary study were contacted, given an MRI eligibility screener, and scheduled by a research coordinator. Written HIPAA and informed consent were provided by all participants. They were then seen by a physician at the University of Maryland General Clinical Research Center for a brief medical evaluation to identify any acute medical problems since their last HANDLS visit, re-administer the MRI eligibility checklist, review current medications, assess whether there were any contraindications to the performance of HANDLS SCAN testing, and complete a brief physical function assessment. The subjects then underwent MRI acquisition in the Department of Diagnostic Radiology & Nuclear Medicine at the University of Maryland School of Medicine. The IRBs of the University of Maryland, Baltimore and the University of Maryland, Baltimore County approved the HANDLS SCAN study. Participation was compensated with $50.

Measures

APOE

Of the HANDLS participants in the study, 1,024 were successfully genotyped to 907,763 single nucleotide polymorphisms (SNPs) at the equivalent of Illumina 1M array coverage. HANDLS participant genotypes were imputed using MACH/minimac version 2.0 (https://genome.sph.umich.edu/wiki/Minimac) based on combined haplotype data for the 1000 Genomes Populations project phase 3 version 5 multi-ethnic reference panel. Exclusion criteria for the genetic sampling included discordance between self-reported sex and sex estimated from X-chromosome heterogeneity, cryptic relatedness, discordance between self-reported African ancestry and ancestry confirmed by genetic data. SNP exclusion criteria were (1) Hardy-Weinberg equilibrium p-value <10–7, minor allele frequency <0.01, and call rate <95%. Genotype quality control and data management was conducted using PLINKv1.06 (PMID: 17701901). Cryptic relatedness was estimated via pairwise identity by descent analyses in PLINK and confirmed using RELPAIR (PMID: 11032786). APOE ε4 status is defined as Yes = 1 or 2 APOE ε4 alleles; No = no APOE ε4 alleles.

Magnetic Resonance Imaging Acquisition.

Participants underwent MRI using a Siemens Tim-Trio 3.0 Tesla scanner. In addition to the standard brain imaging protocol—which includes axial T_1, T_2, FLAIR images—a high resolution axial T_1-weighted- magnetization prepared rapid gradient echo (MPRAGE) (TE = 2.32 ms, TR = 1900ms, TI = 900ms, flip angle = 9º, resolution = 256 × 256 × 96, FOV = 230 mm, sl. Thick. = 0.9 mm) covering the entire brain is acquired and used both as an anatomic reference and to extract parameters of regional, whole brain

volumes and cortical thickness. The T_1-weighted MP-RAGE images covered the entire brain in the sagittal plane at 1.2 mm thickness for a total of 160 slices (TR/TE/TI = 2300/2.9/900 ms; FOV 25.6cm). For comparison purposes, these images were converted from sagittal to axial sections.

In-house techniques developed by the Section for Biomedical Image Analysis at the University of Pennsylvania were used to preprocess structural MRI scans. First, skull-stripping was applied to remove extra-cranial material on the T_1-weighted images using, a multi-atlas registration based method that requires minimal manual correction (Doshi et al., 2013). Bias correction was performed using the multiplicative intrinsic component optimization (MICO) method (Li et al., 2014).

***Pattern Analysis*:**

Dr. Davatzikos has developed high-dimensional pattern analysis methods using machine-learning techniques to summarize complex imaging patterns of structural brain changes along a single dimension. The SPARE-AD index was introduced to identify and quantify AD-like patterns of brain atrophy from MRI images using a multivariate pattern classification method.

Derivation of SPARE-AD Index

Supervised machine learning methods offer unique potential to derive neuroimaging biomarkers for early diagnosis (e.g., patients vs healthy controls). The main components of a supervised classification methodology are feature extraction, feature selection, model training, and application of the learned model on new samples. This computer-based classification method relies on individual patient analysis, aiming to categorize individual scans belonging to participants with AD against those that are cognitively normal in the ADNI (Davatzikos et al., 2009; Fan et al., 2008). This approach

considers all brain regions together and identifies a minimal set of regions whose volumes optimally differentiate between those with AD and those that are cognitively normal on an individual scan basis (Davatzikos et al., 2009; Fan et al., 2008). This classification method creates an algorithm that can calculate a SPARE-AD index for an individual and can be (and has been) applied to the MRI measurements of other studies (e.g., the BLSA; Davatzikos et al., 2009; Fan et al., 2008).

The SPARE-AD index (Fan et al., 2005) was introduced for MRI based classification of controls from AD patients, and was built using T_1-weighted structural scans from ADNI; the model outputs a scalar index for a new test sample. More positive SPARE-AD implies a more AD-like pattern of brain atrophy (e.g., hippocampus, amygdala, entorhinal cortex, inferior temporal). The SPARE-AD method obtained a cross-validated classification accuracy of 94.3% for determining AD vs. CN, 74.3% for MCI vs. CN, and 81.8% for AD vs. MCI (Fan et al., 2008). SPARE-AD analysis from ADNI showed that the MCI subgroup identified as AD-like showed a markedly faster rate of Mini-Mental State Examination (MMSE) decline (Fan et al., 2008b). In applying the classifier to the BLSA, the frequency of more Alzheimer's disease-like SPARE-AD values in cognitively normal participants was evaluated and compared to RAVENS maps (Davatzikos et al., 2009). Group comparisons were performed via voxel-based statistical analysis software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) of respective RAVENS maps that were normalized by an approximation to the total intracranial volume, and this approximation was employed in this analysis for consistency with the approach used in the development of the ADNI classifier. Applying the classifier developed on the ADNI sample to all longitudinal MRI scans of the BLSA cognitively

normal and MCI individuals provided insight on longitudinal SPARE-AD progression (Davatzikos et al., 2009). Data from the BLSA indicated that MCI was related to significantly steeper rate of progression of SPARE-AD score than controls (Davatzikos et al., 2009). This classifier was applied to the HANDLS SCAN images similarly.

Cognitive Measures

Neuropsychological measures spanning multiple cognitive domains were administered via trained psychometrists that were under the supervision of a neuropsychologist. The psychometrists underwent extensive training with the neuropsychologist or other previously trained examiners including several practice sessions to guarantee accurate and reliable administration of the measures in an appropriate manner. Descriptions of the measures, their associated administration procedures, and the reliability and validity for each test are provided below.

Semantic Fluency

This semantic fluency test evaluates the spontaneous production of words of a given category within a minute, and the subject must respond as quickly as possible. The semantic category in this test is animals. Scores on this task were the sum of all admissible animals. Perseverations, proper nouns, variations, or errors were not counted in the total score. This test requires executive strategies of clustering and set shifting to different clusters (Spreen & Straus, 1998; Strauss et al., 2006). Learning about clustering elucidates a subject's search strategies, while set shifting (or switching) reveals a subject's ability to switch between clusters (Troyer et al., 1997). Gaps in stored knowledge, low executive function, or inefficient search strategies could result in deficient performance on this test. Lower educational attainment, literacy, and greater age

are also associated with deficient performance on this test (Strauss et al., 2006). Furthermore, race and ethnicity are associated with performance, such that African Americans perform at a lower level even after accounting for literacy, SES, and education (Alvarez & Emory, 2006). The test has near high inter-rater reliability and test-retest reliability, with coefficients ranging from .70 and .88 (Spreen & Straus, 1998; Strauss et al., 2006). Scores on these tasks correlate with tests of working memory (Rosen & Engle, 1997).

The California Verbal Learning Test

The California Verbal Learning Test (CVLT) is a test that assesses verbal learning and memory, which is administered by presenting orally two different word lists (List A and List B) that each contain 16 items and 4 words from each of four semantic categories (Delis et al., 1987). Normally immediate recall of List A for five trials is required, followed by a one-time presentation and immediate recall of List B. Immediately following the trial with List B, free recall and semantically cued recall are measured. This is repeated after a 20-min delay during which nonverbal tasks are administered. Afterwards the 16 items from List A are asked to be recognized from a larger list that contains several other items not from List A. Then another 10-min delay with nonverbal tasks is administered (Delis et al., 1987). In the HANDLS study only three learning trials were administered, and the cued recall trials were not administered. Total performance on the CVLT is summarized in a total score for the immediate recall across the three trials of List A, as well as total scores from short and long free recall (Delis et al., 1987).

Values of internal consistency of this instrument ranged from .68 to .94, averaged across all ages in the standardization sample with adequate test-retest validity (Delis et

al., 1987). According to Dotson et al., (2009) education and literacy were significant predictors of CVLT trials 1-3 and CVLT long delay free recall in high SES Whites. In contrast, reading scores were a predictor of CVLT outcome for low-SES African Americans and Whites, as well as high-SES African Americans (Dotson et al., 2009).

Sociodemographic Variables

Poverty status is a dichotomous variable where income below 125% of the federal poverty threshold is coded as 1, and income at or above 125% of the poverty threshold was coded as 0. Sex was phenotypically observed, confirmed by chromosomal analysis, and dichotomous (0 = female and 1 = male). Race was self-reported and dichotomous (0 = White and 1 =African American). Literacy was measured using the total Reading score of the Wide Range Achievement Test, Version 3 (WRAT-3), a widely validated and commonly used measure of general literacy and academic achievement, with a test-retest reliability range of .91-.95 (Strauss et al., 2006). The WRAT-3 Reading subtest measures participants' ability to recognize and name letters and words. Age is a continuous variable and was calculated from the participant's birthdate.

Data Analyses

Power analysis

Post hoc power analysis was conducted using G*Power 3.1.3 statistical software. The estimate was based on an *F*-test Linear multiple regression: Fixed model, R^2 increase analysis. For the analysis of Semantic Fluency outcomes, a sample size of 158 with two predictors of interest (APOE ε4 status × Race, SPARE-AD × Race), and nine total predictors (four covariates, APOE ε4 status, SPARE-AD, Race, and their interaction terms) was used. For medium effects to be detected (f^2 estimate of 0.15), using an *a* =

0.05, a power of .99 was achieved. For small effects to be detected (f^2 estimate of 0.02), using an a = 0.05, a power of .33 was achieved. For the analysis of CVLT outcomes, a sample size of 140 (the smallest sample from CVLT outcomes) with two predictors of interest (APOE ε4 status × Race, SPARE-AD × Race), and up to nine total predictors (four covariates, APOE ε4 status, SPARE-AD, Race, and associated interaction terms) were used. For medium effects to be detected (f^2 estimate of 0.15), using an a = 0.05, a power of .98 was achieved. For small effects to be detected (f^2 estimate of 0.02), using an a = 0.05, a power of .30 was achieved. This demonstrates that adequate power can be achieved from these analyses in order to detect a moderate, but not small effect in this sample. That said, this power analysis provides a gross estimation, as F statistics are not examined. Moreover, given the relative absence of prior literature conducting similar models, an expected effect size was not estimated.

Descriptive statistics

Prior to beginning any analyses, descriptive statistics were computed. Normality, skewness, outliers, and multicollinearity were evaluated for these variables, as well as for the cognitive measures. Raw scores were used for the analyses. Any skewed distributions of variables were log-transformed to normalize them, and the variable distributions were visualized via histograms.

Moderated Mediation Analyses

To test all four hypotheses, several moderated mediation analyses (Process Model 59) were run. APOE ε4 status served as the primary predictor, select tests of cognitive performance (i.e., Semantic Fluency data, CVLT total score, CVLT short free recall, and CVLT long free recall) served as the outcome variables, race served as the moderator,

and the SPARE-AD index served as the mediator (Figure 1). Separate analyses were run for each measure of cognitive performance. This yielded a total of four moderated mediation models. Poverty status, literacy, sex, and age were used as covariates for all analyses.

Mediation analyses were run using PROCESS (Hayes, 2013) on R (version 3.6.3; R Core Team, 2015). Within PROCESS, model 59 (moderated mediation model with one mediator and one moderator) was specified. PROCESS provided the output for the following three linear regressions:

1) Predictors: APOE ε4 status × Race, APOE ε4 status, race, poverty status, literacy, sex, and age; Outcome: Four Cognitive Performance measures (i.e., Semantic Fluency, CVLT total score, CVLT short free recall, and CVLT long free recall)

2) Predictors: APOE ε4 status × Race, APOE ε4 status, race, poverty status, literacy, sex, and age; Outcome: SPARE-AD

3) Predictors: SPARE-AD × Race, APOE ε4 status × Race, SPARE-AD, race, APOE ε4 status, poverty status, literacy, sex, and age; Outcome: Four Cognitive Performance measures (Semantic Fluency, CVLT total score, CVLT short free recall, and CVLT long free recall)

These regressions produced the total, direct, and indirect effects of the model, which were interpreted. Effect sizes were calculated by taking the ratio of indirect effect to total effect (direct + indirect effects) of X on Y (Hayes, 2013).

Results

Description of Sample

The analysis sample included 165 African American and White, urban dwelling adults; however, analysis-specific samples varied based on complete performance for the cognitive measures (Table 1). Thus, the current analyses utilized 158 participants in the Semantic Fluency analysis and 140 participants across the CVLT analyses. On average, participants were middle-aged with a mean age of 53.4 years for the Semantic Fluency sample and 53 years for the CVLT analyses. In the Semantic Fluency analysis, 35.4% of the sample were African American, 57% were female, and 31% had income below 125% of the federal poverty threshold. Similarly, for participants across the CVLT analyses, 37.9% were African American, 55.7% were female, and 34.3% had income below 125% of the federal poverty threshold. Preliminary data screening suggested that there were no violations of assumptions of normality and linearity. The bivariate and point-biserial correlations among all the study variables are demonstrated in Table 2. The Semantic Fluency sample (Table 3) and CVLT sample (Table 4) were also split by race to compare differences in characteristic distributions.

Main Hypotheses

Several moderated mediation models were computed to examine whether the association of APOE ε4 status and AD-associated cognitive outcomes is mediated by SPARE-AD and if that relationship is moderated by race while covarying for age, sex, poverty status, and literacy. All coefficients reported were unstandardized, with $\alpha = .05$ two-tailed as the criterion for statistical significance. Effect sizes were computed for all mediations by calculating the ratio of the indirect effect to total effect of X on Y (Hayes,

2013). For all of the mediations, the independent variable was APOE ε4 status. The mediating variable was the MRI-assessed AD risk pattern of brain atrophy (SPARE-AD) for all analyses. The outcome variables assessed (in separate analyses) were the Semantic (Animal) Fluency test and the California Verbal Learning Test (CVLT total, short free recall, and long free recall). To test the indirect effects of all mediations (*ab*), bootstrapping CIs were performed with 5,000 samples. Complete results are outlined in Tables 5-14, and all models are demonstrated in Figure 4.

Model 1 – APOE ε4 status, SPARE-AD, Race, and Semantic Fluency.

Model 1 assessed whether race moderated the indirect effect of APOE ε4 status on Semantic Fluency via the SPARE-AD while controlling for age, sex, poverty status, and literacy. There was a significant interaction of race × APOE ε4 status on Semantic Fluency (c_3' path), B = -4.05, t(157) = -2.39, $p < .05$, wherein 3.25% of the variance was accounted for by the interaction. The conditional direct effect of having one or two APOE ε4 alleles was associated with better levels of performance on the Semantic Fluency measure (Figure 2), but was only significant for Whites (3.65, t(157) = 3.05, $p <$ .01) and not for African American participants (-.40, t(157) = -.34, p = .74). The interaction of race ×APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD (a_3 path), B = -0.20, t(157) = -0.76, p = .45. There was also no significant effect of APOE ε4 status (a_1 path) or race (a_2 path) individually on the mediator. When controlling for the interaction of race × APOE ε4 status, the interaction of race × SPARE-AD (b_2) was not significantly associated with Semantic Fluency, B =1.66, t(157) = 1.41, p = .16. The indirect effect, *ab*, for White participants was -0.16, and the lower and upper limits were -0.86 and 0.48, respectively; while, for African

American participants it was -0.0163 and the lower and upper limits were -0.59 and 0.28, respectively. As the bootstrapped CI include zero, the indirect effect at both levels of the moderator were not statistically significant. Therefore, the effect of race × APOE ε4 status on Semantic Fluency was not mediated by SPARE-AD.

Model 2 – APOE ε4 status, SPARE-AD, Race, and California Verbal Learning Test (total).

Model 2 assessed whether race moderated the indirect effect of APOE ε4 status on CVLT total word recall via the SPARE-AD while controlling for age, sex, poverty status, and literacy. There was no significant interaction of race × APOE ε4 status on CVLT total (c_3' path), B = -2.65, t(157) = -1.01, p = .27. There was also no significant effect of APOE ε4 status (c_1' path) or race (c_2' path) individually on CVLT total. The interaction of race ×APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD (a_3 path), B = -0.09, t(157) = -.32, p = .75. There was also no significant effect of APOE ε4 status (a_1 path) or race (a_2 path) individually on the mediator (across all CVLT analyses). When controlling for the interaction of race × APOE ε4 status, the interaction of race × SPARE-AD was not significantly associated with CVLT total (b_2 path), B =0.15, t(157) = 0.09, p = 0.93. The indirect effect, ab, for White participants was -0.03, and the lower and upper limits were -0.92 and .44, respectively; while, for African American participants it was -0.001 and the lower and upper limits were -0.55 and 0.27, respectively. As the bootstrapped CI include zero, the indirect effect at both levels of the moderator were not statistically significant. Therefore, the effect of race × APOE ε4 status on CVLT total was not mediated by SPARE-AD.

Model 3 – APOE ε4 status, SPARE-AD, Race, and CVLT (short free recall).

Model 3 assessed whether race moderated the indirect effect of APOE ε4 status on CVLT short free-recall via the SPARE-AD while controlling for age, sex, poverty status, and literacy. There was a significant interaction of race × APOE ε4 status on CVLT short free-recall (c_3' path), B = -2.46, t(157) = -2.18, p < .05, wherein 2.67% of the variance was accounted for by the interaction. The conditional direct effect of having one or two APOE ε4 alleles was associated with worse levels of performance on CVLT short free-recall (figure 3) but was only significant for African American participants (-1.98, t(157) = -2.53, p < .05) and not for White participants (.47, t(157) = 0.58, p = 0.56). The interaction of race ×APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD (a_3 path), B = -0.09, t(157) = -0.32, p = 0.75. When controlling for the interaction of race × APOE ε4 status, the interaction of race × SPARE-AD was not significantly associated with CVLT short free-recall (b_2), B =-0.15, t(157) = -0.19, p = 0.85. The indirect effect, *ab*, for African American participants was -.003, and the lower and upper limits were -0.26 and 0.17, respectively; while, for White participants it was -0.019 and the lower and upper limits were -0.34 and 0.26, respectively. As the bootstrapped CI include zero, the indirect effect at both levels of the moderator were not statistically significant. Therefore, the effect of race × APOE ε4 status on CVLT short free-recall was not mediated by SPARE-AD.

Model 4 – APOE ε4 status, SPARE-AD, Race, and CVLT (long free recall).

Model 4 assessed whether race moderated the indirect effect of APOE ε4 status on CVLT long free recall via the SPARE-AD while controlling for age, sex, poverty status, and literacy. There was no significant interaction of race × APOE ε4 status on

CVLT long free recall (c_3' path), B = -1.93, t(157) = -1.83, p = .07. There was also no significant effect of APOE ε4 status (c_1' path) or race (c_2' path) individually on CVLT long free recall. The interaction of race ×APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD (a_3 path), B = -0.09, t(157) = -0.32, p = 0.75. When controlling for the interaction of race × APOE ε4 status, the interaction of race × SPARE-AD was not significantly associated with CVLT long free recall (b_2), B =-1.14, t(157) = -1.57, p = 0.12. The indirect effect, ab, for White participants was .02, and the lower and upper limits were -0.22 and 0.35, respectively; while, for African American participants it was -0.01 and the lower and upper limits were -0.40 and 0.32, respectively. As the bootstrapped CI include zero, the indirect effect at both levels of the moderator were not statistically significant. Therefore, the effect of race × APOE ε4 status on CVLT total was not mediated by SPARE-AD.

Exploratory Analyses

Several sensitivity analyses were performed to examine whether the association of APOE ε4 status and AD-associated cognitive outcomes is mediated by SPARE-AD in an African American only sample while covarying for age, sex, poverty status, and literacy. Due to these exploratory analyses using a subset of the initial sample (only the African American participants), the exploratory samples were significantly reduced, with 56 participants in the Semantic Fluency analysis and 53 participants across the CVLT analyses. For large effects to be detected in the Semantic Fluency sample (f^2 estimate of 0.35), using an a = 0.05, a power of .977 was achieved. For medium effects to be detected (f^2 estimate of 0.15), using an a = 0.05, a power of .712 was achieved. Meanwhile, for large effects to be detected in the CVLT samples (f^2 estimate of 0.35),

using an a = 0.05, a power of .970 was achieved. For medium effects to be detected (f^2 estimate of 0.15), using an a = 0.05, a power of .684 was achieved. Despite being underpowered compared to the initial hypotheses, these exploratory analyses provided insight regarding the mediational process within the original models.

Model 1a – APOE ε4 status, SPARE-AD, and Semantic Fluency in African American only Sample.

Model 1a assessed the indirect effect of APOE ε4 status on Semantic Fluency via the SPARE-AD in an African American only sample while controlling for age, sex, poverty status, and literacy. The total effect of APOE ε4 status on Semantic Fluency was not significant, c = -0.33, t(55) = -0.3, p =.77. APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD, a = -0.005, t(55) = -0.04, p = .97. When controlling for APOE ε4 status, SPARE-AD was not significantly associated with Semantic Fluency, b =0.19, t(54) = 0.17, p = .87. The estimated direct effect of APOE ε4 status on Semantic Fluency, controlling for SPARE-AD was c' = -0.33, t(54) = -0.3, p = .77. The indirect effect, ab, was -0.0010, and the lower and upper limits were -0.4859 and 0.3057, respectively. As the bootstrapped CI include zero, the indirect effect of APOE ε4 status on Semantic Fluency through SPARE-AD was not statistically significant. Therefore, the effect of APOE ε4 status on Semantic Fluency was not mediated by SPARE-AD in an African American only sample.

Model 2a – APOE ε4 status, SPARE-AD, and California Verbal Learning Test (total) in African American only Sample.

Model 2a assessed the indirect effect of APOE ε4 status on CVLT total via the SPARE-AD in an African American only sample while controlling for age, sex, poverty

status, and literacy. The total effect of APOE ε4 status on CVLT total was not significant, c = -1.56, t(53) = 0.11, p =.91. APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD, a = 0.017, t(55) = -0.04, p = .97. When controlling for APOE ε4 status, SPARE-AD was not significantly associated with CVLT total, b =-0.65, t(52) = -0.45, p = .65. The estimated direct effect of APOE ε4 status on CVLT total, controlling for SPARE-AD was c' = -1.55 t(52) = -1.05, p = .30. The indirect effect, ab, was -0.0109, and the lower and upper limits were -0.8165 and 0.2663, respectively. As the bootstrapped CI include zero, the indirect effect of APOE ε4 status on CVLT total through SPARE-AD was not statistically significant. Therefore, the effect of APOE ε4 status on CVLT total was not mediated by SPARE-AD in an African American only sample.

Model 3a – APOE ε4 status, SPARE-AD, and CVLT (short free recall) in African American only Sample.

Model 3a assessed the indirect effect of APOE ε4 status on CVLT short free-recall via the SPARE-AD in an African American only sample while controlling for age, sex, poverty status, and literacy. The total effect of APOE ε4 status on CVLT short free-recall was significant, c = -2.01, t(53) = -3.14, p < .01. APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD, a = 0.017, t(53) = 0.11, p = .91. When controlling for APOE ε4 status, SPARE-AD was not significantly associated with CVLT short free-recall, b = -0.49, t(52) = -0.78, p = .44. The estimated direct effect of APOE ε4 status on CVLT short free-recall, controlling for SPARE-AD was c' = -2.0, t(52) = -3.11, p < .01. The indirect effect, ab, was -0.0082, and the lower and upper limits were -0.3501 and 0.1922, respectively. As the bootstrapped CI

included zero, the indirect effect of APOE ε4 status on CVLT total through SPARE-AD was not statistically significant. Therefore, the effect of APOE ε4 status on CVLT short free-recall was not mediated by SPARE-AD in an African American only sample.

Model 4a – APOE ε4 status, SPARE-AD, and CVLT (long free recall) in African American only Sample.

Model 4a assessed the indirect effect of APOE ε4 status on CVLT long free-recall via the SPARE-AD in an African American only sample while controlling for age, sex, poverty status, and literacy. The total effect of APOE ε4 status on CVLT long free-recall was significant, c = -1.6, t(53) = -2.40, $p < .05$. APOE ε4 status was not significantly associated with the mediating variable, SPARE-AD, a = 0.017, t(53) = 0.11, p = .91. When controlling for APOE ε4 status, SPARE-AD was not significantly associated with CVLT long free-recall, b = -1.22, t(52) = -1.92, p = .06. The estimated direct effect of APOE ε4 status on CVLT long free-recall, controlling for SPARE-AD was c' = -1.58, t(52) = -2.43, $p < .05$. The indirect effect, ab, was -0.0203, and the lower and upper limits were -0.5258 and 0.3818, respectively. As the bootstrapped CI included zero, the indirect effect of APOE ε4 status on CVLT long free-recall through SPARE-AD was not statistically significant. Therefore, the effect of APOE ε4 status on CVLT long free-recall was not mediated by SPARE-AD in an African American only sample.

Discussion

The present study examined whether the association of APOE ε4 status and AD-associated cognitive outcomes was mediated by SPARE-AD – a MRI-assessed AD risk pattern of brain atrophy -and if the entire model was moderated by race. This model was adjusted for poverty status, literacy, sex, and age in a sample of socioeconomically

diverse urban-dwelling African American and White adults (Figure 1). The cognitive outcomes measured were the Semantic (Animal) Fluency test and the California Verbal Learning Test (total, short free recall, and long free recall). Analysis-specific samples varied based on complete performance for each cognitive measure, with 158 participants in the Semantic Fluency analysis and 140 participants across the CVLT analyses. Specifically, it was hypothesized that: 1) Race would moderate the relation of APOE ε4 status to cognitive function such that Whites with APOE ε4 would have lower levels of performance on cognitive outcomes than Whites with non-APOE ε4 status. A similar, but less pronounced relation was expected among African Americans; 2) Race would moderate the relation of APOE ε4 status to SPARE-AD such that Whites with APOE ε4 would have higher levels of SPARE-AD than Whites with no APOE ε4 alleles. A similar, but less pronounced relation was expected among African Americans; 3) Race would moderate the relation of SPARE-AD score to cognitive function such that Whites with greater SPARE-AD would have lower levels of cognitive function than Whites with lower SPARE-AD. A similar, but potentially more pronounced relation was posited among African Americans; 4) The significant interactive relation of race and APOE to cognitive function would be mediated by SPARE-AD (i.e., moderated mediation).

The results did not support the study hypotheses. Overall, the findings revealed few significant associations (Table 5-14). Hypothesis one was partially supported, in that race moderated the relation of APOE ε4 status to cognitive performance on two of the four outcome measures; however, not in the direction that was expected. Specifically, race moderated the relation of APOE ε4 status to semantic fluency; however, when the interaction was probed, the relation was only significant for Whites. Unexpectedly, White

carriers of ε4 performed better than non-carriers. Conversely, race moderated the relation of APOE ε4 status to CVLT short free-recall whereby, African-American ε4 carriers performed worse than African American non-carriers. Hypotheses two, three, and four were not supported in any of the models. Further exploratory analyses were conducted to examine if the association of APOE ε4 status and AD-associated cognitive outcomes was mediated by SPARE-AD in an African American-only sample while covarying for age, sex, poverty status, and literacy. These analyses similarly revealed that relations of APOE ε4 status to cognitive outcome measures were not mediated by SPARE-AD among African Americans. The study's significant and null findings for each path of the mediational model will be discussed in detail below.

Race × APOE ε4 and Cognitive Performance (c_3' path)

For the first hypothesis, it was expected that race would moderate the relation of APOE ε4 status to cognitive function, such that Whites with APOE ε4 would have lower levels of performance on cognitive outcomes than Whites with non-APOE ε4 status. A similar, but less pronounced relation was expected among African Americans. Results demonstrated mixed findings, with race moderating the relation of APOE ε4 status to semantic fluency (Animals) and CVLT short free-recall. However, the ε4-semantic fluency relation was only significant for Whites and—unexpectedly—White carriers of ε4 performed better than non-carriers. In contrast, for the ε4-CVLT short free-recall relation, African-American ε4 carriers performed worse than African American non-carriers. Remaining results yielded null findings, with no significant interactive relations of race and APOE ε4-to CVLT long free-recall or total free-recall and no significant main effects (c_1'and c_2'paths). In the mediation model for the exploratory analyses, APOE ε4

status was not significantly associated with any cognitive measures in an African American only sample (c' path), except for CVLT short and long free recall.

Domain-specific inconsistencies among APOE-cognition relations have been documented in other studies, especially when comparing the effect of APOE ε4 allele status on memory versus other domains of cognition like verbal fluency or attention (Beydoun et al., 2021). However, it should be noted that the literature is sparse and mixed regarding the preclinical association of APOE ε4 status and cognitive performance, especially within the context of variation by self-identified race (Alzheimer's Association, 2021). Yet, even taking this into consideration, the results of the current study are inconsistent compared with the findings in the broader literature. As discussed previously, the expectation was that ε4 status precipitates reduced performance in cognitive tasks, thus the ε4-fluency relation among White participants is inconsistent with the general literature. Additionally, the notion that the strength of the ε4-cognition relation differs by race has indeed been seen before: in an early meta-analysis it was found that the ε4 allele was only weakly associated with AD risk among African Americans, but strongly associated in Whites (Farrer et al., 1997). This implies that while the ε4 allele is still harmful for African Americans in terms of AD-pathophysiology, it is not as severe as it is for Whites. This trend was only partially seen in the current study, as the ε4-short free-recall relation demonstrated poorer performance for ε4 carriers in African Americans but yielded no significant relation in White participants.

Other research suggests that the APOE ε4 allele predicts cognitive decline for both African Americans and Whites (Sawyer et al., 2009). In a methodologically sound examination of over 2,076 participants spanning a 10-year period, results of multilevel

models for repeated measures revealed that the occurrence of at least one ε4 allele was associated with increased cognitive errors on the Short Portable Mental Status Questionnaire (SPMSQ) at wave 1, as well as a more rapid decline in cognitive function over time, regardless of race (Sawyer et al., 2009). African Americans, however, experienced a faster rate of cognitive decline than Whites, regardless of ε4 carrier status. This study would generally support one of the findings of the present investigation, wherein African-American ε4 carriers performed worse than African American non-carriers on CVLT short recall; yet the lack of association in Whites in the present study is not consistent with the aforementioned literature. Differences between the previous study and the present project, however, were the specificity of the cognitive measures used, and the longitudinal versus cross-sectional designs. It is worth noting that a recent review of the literature examining the association between the APOE ε4 allele and cognition revealed mixed results, with some studies finding a relationship and others finding no association (O'Donoghue et al., 2018). Because a clear pattern has not yet been established, the review highlighted the significance of using domain-specific neuropsychological batteries due to the lack of sensitivity or specificity of many cognitive measures to subtle variations in cognition or changes in specific domains. Some studies have shown associations between ε4 and cognition in certain domains but not all, emphasizing the importance of AD-specific cognitive correlates rather than global cognitive screeners.

A longitudinal study that utilized memory measures was conducted by Mormino and colleagues (2014) on 490 cognitively normal older adults from the ADNI and AIBLS samples. The study tracked the impact of APOE ε4 carrier status and amyloid-β (Aβ) on

cognitive decline over a median follow-up period of nearly 1.49 years. Higher Aβ deposition was associated with increased likelihood of ε4 carrier status, and the steepest decline in cognitive performance was observed in ε4 carriers with high Aβ. Cognitive decline was assessed via performance on the MMSE and the immediate and delayed recall scores from the Logical Memory test. The authors suggested that ε4 carriership may impact cognitive outcomes through neuroanatomical pathways beyond amyloidosis. Although this study used the Logical Memory Test, this measure differs from the present study's use of the CVLT, as the former is a measure of contextual story memory, and the latter focuses on list learning and list recall.

Furthermore, the study by Mormino and colleagues (2014) also utilized a global screener which, as previously noted, has been identified as a weaker measure for tracking cognition within the literature (O'Donoghue et al., 2018). The use of global screening measures to dichotomously classify outcomes based on impairment provides a fast and convenient approach for estimating overall cognitive status; however, more robust neuropsychological tests better measure specific domains of function that are impacted by AD pathophysiology. Moreover, the use of screening measures is linked to measurement bias, as studies have reported that standardized screening tests for dementia have higher false-positive rates for African Americans than Whites (Fillenbaum et al., 1990; Sawyer et al., 2009). It is also relevant that the longitudinal study relied on an older sample, which would produce much more stark changes in cognition compared to the middle-aged cohort of the current investigation.

In a longitudinal study, with a longer follow-up period, of a sample of 84 cognitively normal older adults with high Aβ deposition (Lim et al., 2015) it was found

that ε4 carriers with high levels of Aβ showed significantly faster decline on memory domains than non-carriers. In fact, the study found that in healthy older adults without the ε4 allele, there was very little decline in memory and no decline in attention or psychomotor function over a 54-month period, even when they had high levels of Aβ (Lim et al., 2015). Therefore, the results suggest that amyloidosis is linked to a decline in memory but that this decline is influenced by ε4 carriership, which implies an interaction between ε4 and brain measures (in this instance amyloidosis) on cognitive outcomes. A notable caveat is that this study relied on the Cogstate Brief Battery, MMSE, and the Clinical Dementia Rating scales, which again skew towards a more global gestalt of cognitive performance and lacks some of the sensitivity of the measures used in the present study, like the explicit memory measure CVLT or a more executive and semantic language test like the Animal Fluency test. This further distinguishes the differences between the present study and much of the literature on ε4-cognition relations. It is also worth noting that the review by O'Donoghue and colleagues (2018) does not discuss potential racial disparities in the ε4-cognition literature and the possible differential impact of the ε4 allele on cognition in this context.

Yet, according to Hendrie and colleagues (2014), the presence of the ε4 allele is associated with an increased risk of AD-pathophysiology in African Americans, regardless of whether the carrier is homozygous or heterozygous. Interestingly, the association was weaker in a Nigerian sample, and only homozygosity for the ε4 allele was associated with AD risk. This finding was surprising given the higher prevalence of carrier status in the African group. Thus, it was hypothesized by Hendrie and colleagues (2014) that the weaker association in the Nigerian group as compared to the African

American sample may be due to stressors and lifestyle exposures or genetic differences resulting from the admixture of African and European ancestry in most African American samples. These factors (stressors, lifestyle factors, admixture of ancestry) may also be influencing the results in the present study as they were not identified as covariates.

Also relevant are the findings of a study that examined the ancestry of the ε4 allele in African American and Puerto Rican populations and discovered that the ε4 allele in the African-ancestral region conferred a lower risk for AD than those with a European ancestor allele, regardless of population (Rajabli et al., 2018). This implies that APOE ε4 alleles derived from African ancestry may be more protective against AD risk than those derived from European ancestry. This research suggests that in the context of ε4 carrier status, African ancestry may be protective against AD, whereas European ancestry may be a risk factor, which led to the development of Hypothesis 1 for the present study. Although the results of the present analyses were not aligned with this conceptualization of the genetic underpinnings of ε4 among African Americans, it is imperative to understand that the present study did not have genetic data available at the time pertaining to the ancestral origin of the ε4 allele. It was merely assumed that African Americans had a higher likelihood of the ε4 allele being inherited from African ancestry compared to Whites. This perspective suggested that independent of socioeconomic stressors or other lifestyle factors encountered by African Americans, ancestral race could be a variable that modifies the relation between ε4 and AD risk. This led to the hypothesis that as a whole, African Americans would have an attenuated yet still present ε4-cognitive function association in the current study. This may still be a contributing

factor to some of the inconsistent findings regarding the impact of the ε4 allele on cognition in African American samples.

It has previously been suggested that insufficient sample size, a low percentage of African American participants, the use of dichotomous measures of cognition, and not properly adjusting for SES factors have led to the mixed findings within the literature (Sawyer et al., 2009). Yet, many studies have also found little to no ε4-cognition associations in African Americans compared to White Americans (Borenstein et al., 2006). Instead of an ancestral origin perspective, one hypothesis implies that the ε4 allele impacts both African Americans and Whites equally, but that complex biological, sociocultural, and contextual factors—like racial discrimination, food insecurity, neighborhood disorder—make the relation difficult to parse out in African Americans because of the unique experiences of this group. African Americans have experienced distinct hardships that may contribute to health and cognitive disparities compared to their White counterparts. These disparities may be due to lack of resources, cultural differences, chronic exposure to harmful stimuli, assessment bias, and discrimination (Dimsdale, 2008; Graff-Radford et al., 2016; Profant & Dimsdale, 1999; Shonkoff et al., 2009; Tomfohr et al., 2016). The physiological stress response resulting from discrimination and other systemic factors may impact the immune system, exacerbate cardiovascular disease risk factors, and result in cognitive decline (Dimsdale, 2008; Profant & Dimsdale, 1999; Shonkoff et al., 2009; Tomfohr et al., 2016). Systemic barriers surrounding socioeconomic opportunities and differences in quality of education and literacy may also contribute to cognitive performance disparities between African Americans and Whites (Avila et al., 2021; Mehta et al., 2010; Sachs-Ericsson & Blazer,

2005; Weuve et al., 2018; Yaffe et al., 2013). In fact, in the present study almost 45% of the African Americans in the Semantic Fluency sample had income below 125% of the federal poverty threshold, while only about 26% of Whites fit that category (Table 3); potentially implying that other aspects of SES in the current analyses may influence the ε4 association with cognitive performance among African Americans. This disparity is also reflected in the CVLT samples (Table 4) and may call into question if enough SES variables were adjusted in the current study to take into account their impact on cognitive reserve.

As the present study directly incorporated modifications to address some of the limitations of previous literature, and in the absence of ancestral data, the current findings suggest that African Americans with at least one ε4 allele have reduced performance on a memory task. This aligns with some of the literature that suggests ε4-cognition relations in African Americans share directionality with findings of Whites (Gottesman et al., 2017; Hendrie et al., 2014; Sawyer et al., 2009). However, the current findings also highlight that perhaps ancestral race could be a more accurate variable to use for the exploration of potential moderation in the relation between ε4 and cognitive performance (Rajabli et al., 2018). On the other hand, these findings and the implications of the aforementioned literature may suggest that perhaps race itself is a poor proxy for all the social determinants of health that it is thought to index. Future avenues may benefit from directly looking at racial discrimination, neighborhood disorder, lack of resources, diet, SES, and/or exposure to harmful stimuli as the primary moderator for the relation of APOE ε4 status to cognitive function. This may help clarify some of the unexpected

findings of the current study that centered on race and its impact on ε4-cognition relations.

For example, this study also found that White carriers of the ε4 allele performed better than non-carriers on a task of semantic fluency. Some investigators have noted that one of the first clinical manifestations within the AD continuum is semantic memory loss, typically measured via verbal (e.g., semantic, phonemic) fluency and naming (Verma & Howard, 2012). The purported impact on this domain led to the hypothesis that in a preclinical sample, performance on an Animal fluency task would be lower for ε4 carriers than non-carriers. Despite the paradoxical findings of the present project, there is at least one other study that found ε4 carriers to have better verbal fluency performance than non-carriers (Marioni et al., 2016). The study by Marioni and colleagues (2016) examined 18,337 participants from the Generation Scotland study, ranging in age from 18 to 94 years (mean of 47). Within that study, four cognitive domains were evaluated: verbal declarative memory, processing speed, verbal fluency, and vocabulary. As expected, the presence of the ε4 allele was associated with lower scores in memory and processing speed among individuals aged 60 and older (Marioni et al., 2016). Of note is that these findings were noted in older adults and also relied on a story memory measure, further contrasting with the younger population of the present study and the list recall measure used (CVLT). Surprisingly, across all age groups of the Marioni and colleagues (2016) study, the ε4 allele was linked to better performance in verbal fluency and in younger subjects (≤60 years old), the ε4 allele was associated with higher vocabulary scores. The authors of that study acknowledged that the verbal fluency results went counter to their hypothesis and was inconsistent with the general body of literature but suggested that the

distribution of verbal fluency scores resembles those of a more crystallized intelligence measure, and thus would follow a pattern less associated with more fluid measures. A similar paradigm may be applicable to the present study. This could also be an example of antagonistic pleiotropy: where the impact of a gene is advantageous in early life but deleterious in later life. It was originally thought the middle-aged adults may bypass the influence of antagonistic pleiotropy regarding ε4-cognition associations (O'Donoghue et al., 2018), yet for measures of verbal fluency this may not be the case.

Additionally, an early cross-sectional study examining the impact of the ε4 allele on cognitive outcomes in a preclinical sample of 220 White middle-aged participants found that the ε4 allele was significantly associated with diminished performance in the domain of verbal learning and both visual and verbal memory, but not attention or semantic fluency (Flory et al., 2000). Even with the known course of AD progression on semantic fluency, in a meta-analysis of 77 studies, ε4 carriership negatively impacted performance on measures of episodic memory, executive functioning, and overall global cognitive ability; yet had no significant impact on verbal ability, which included measures of semantic fluency (Wisdom et al., 2011). Another potential factor could be that semantic fluency requires executive strategies, such as clustering and set-shifting, and is a task that is heavily influenced by gaps in stored knowledge, low executive function, or inefficient search strategies (Spreen & Straus, 1998; Strauss et al., 2006). Thus, lower educational attainment, literacy, and greater age are also associated with deficient performance on this test (Strauss et al., 2006).

Although in the current study the level of education and poverty status of White ε4 carriers compared to non-carriers were generally comparable, there are a variety of

complex aspects pertaining to stored knowledge that could potentially contribute to performance on semantic fluency, such as the quality of education and level of SES during formative years. This may suggest that measures of semantic fluency may not demonstrate appropriate sensitivity for preclinical samples of ε4 carriership as previously thought and ultimately impact the results of the current study.

Another relevant issue to consider is the varying impact of dose on ε4 carriership and cognition. That is to say, the impact of ε4 homozygosity versus heterozygosity on cognitive performance, which allele configurations are most protective, and how this may vary by race. Although the ε2 allele is thought of as protective against AD and cognitive decline, the ε2/ε4 configuration has been seldom studied at length due to its rarity. In a longitudinal study controlling for age, sex, education, baseline cognitive status, and years of initial visit in an all-White sample, it was found that that the heterozygous combination of APOE ε2/ε4 has a statistically significant association with increased risk of AD and MCI when compared to homozygous ε3/ε3 individuals (Ren et al., 2020). This is contrasted by findings suggesting that in African Americans, the ε2/ε4 configuration does not confer higher AD or MCI risk, and in fact demonstrates a marginal (i.e., not statistically significant) protective factor from cognitive decrement (Ren et al., 2021). This is relevant to the current study because it is possible that only looking at the presence of ε4 carriership might not fully capture the nuance in AD or MCI risk, which in turn speaks to the underlying impact of APOE dosage on ε4-cognition relations.

The APOE dosage specific impact on cognition, and how it may vary by race has also been explored within the HANDLS study previously where Beydoun and colleagues (2021) investigated the impact of APOE2 and APOE4 gene dosages on changes in

neuropsychological test scores measuring different cognitive domains. Their study of 1770 HANDLS participants had similar sample characteristics (mean age = 48.5, 55.1% African American, 57.2% female, 38.9% below poverty status) to the CVLT and Semantic Fluency analyses of the present study. In their mixed-effects linear regression models, the two main exposures were APOE2 and APOE4 dosages, while cognitive performance on 11 test scores in visit 1 and the change in performance from visit 1 to visit 2 were the main outcomes of interest (Beydoun et al., 2021). Within their model, race and sex were first considered as effect modifiers in a minimally adjusted model (age, sex, and poverty status) and then a model adjusted for sociodemographic, lifestyle, and health-related factors (illicit drug use, smoking status, body mass index, educational attainment, literacy, self-rated health status, the Healthy Eating Index 2010, the total score on the 20-item Center for Epidemiological Studies-Depression scale (CES-D), hypertension, diabetes, dyslipidemia, and self-reported history of any of several cardiovascular disease conditions). They found that among Whites only, a higher APOE4 gene dosage was associated with faster decline in verbal memory performance (CVLT-List A), yet among African Americans, specifically African American women, a higher APOE4 gene dosage was linked to slower decline in performance on the Brief Test of Attention (BTA), while no significant association was observed among African American men in relation to APOE4 dosage and changes in BTA over time (Beydoun et al., 2021). Overall, the effects of APOE2 and APOE4 dosages on other cognitive domains were inconsistent and varied across racial groups but did not withstand correction for multiple testing.

It should also be noted that the study by Beydoun and colleagues (2021) used a much larger array of specific and sensitive neuropsychological tests than the present study, and thus found relations in domains that were not expected, such as attention, which may suggest that future studies should probe additional cognitive measures to explore non-AD specific domains that may be secondarily impacted by ε4. Additionally, these findings further provide credence to the impact ε4 dosage has on the ε4-cognition relation, especially within a sample of HANDLS participants, and how this factor may be partially responsible for the findings of the present study.

In fact, in the current moderated mediation study, the vast majority of participants were heterozygous ε4 carriers; which the literature suggests would have a lesser likelihood of conferring the full cognitive consequences compared to homozygous ε4 carriers within the complex context of race (Borenstein et al., 2006; Elahi & Miller, 2017; Masters et al., 2015; Tanzi, 2012; Van Cauwenberghe et al., 2016; Ren et al., 2020; Ren et al., 2021). Among both the Semantic fluency and CVLT samples, there were comparable proportions of ε4 carriers (Table 1). When each sample was further split by race, it was evident that the vast majority of ε4 carriers were the African American participants in the sample, with nearly 45% of African Americans in the Semantic Fluency group carrying the ε4 allele and only about 16% of Whites being carriers (Table 3). Likewise, in the CVLT group, about 47% of African Americans were ε4 carriers and only 17% White participants were ε4 carriers (Table 4).

For the Semantic Fluency sample, 19 White participants had an ε4 allele (12.03 % of total Semantic Fluency sample), and of those, 18 were heterozygous carriers; in contrast, African American participants had 26 ε4 carriers (16.46% of sample), with 22

being heterozygous carriers. For the CVLT sample, 15 White participants had an ε4 allele (10.71% of total CVLT sample), and of those, 14 were heterozygous carriers; in contrast, African American participants in this sample had 25 (17.86% of total CVLT sample) ε4 carriers, with 21 being heterozygous carriers. Overall, these small proportions of ε4 carriers across both races relative to the sample size may mask some of the impact the allele has on outcomes, which indicates that it may be necessary to oversample ε4 carriers in a study like this. Furthermore, although it was expected that African American participants would have a higher ε4 frequency consistent with prior literature (Alzheimer's Association, 2021; Maestre et al., 1995; O'Donoghue et al., 2018; Weuve et al., 2018), it is notable that the African American sample had a higher percentage of homozygous carriers for both samples compared to White participants (CVLT analyses: 16% vs 7%; Animals Fluency analyses: 15% vs 5%). Additionally, African Americans had less of the protective ε3/ε4 carriership compared to White participants (CVLT analyses: 60% vs 73% ; Animals Fluency analyses: 62% vs 79%). The complexities of APOE ε4-cognition relationships by race, the higher distribution of protective ε3/ε4 in White participants for this study, and the lower number of homozygous carriers in White participants may partially explain the findings of the present study.

Overall, exploring the relation of Race × APOE ε4 on cognitive performance yielded results that did not support the proposed hypothesis and were inconsistent with the general APOE ε4 literature. However, because the literature is primarily mixed, there are a few instances in which our results have, to a certain extent, also been observed. For example, it was expected that Whites with APOE ε4 would have lower levels of performance on cognitive outcomes than Whites with non-APOE ε4 status and a similar,

but less pronounced relation was expected among African Americans. What was found was that White ε4 carriers performed better on a measure of verbal fluency than non-carriers; which generally goes against the literature, but has been seen in at least one other study (Marioni et al., 2016). On a measure of verbal short free-recall, African-American ε4 carriers performed worse than African American non-carriers, which would be expected based on some of the literature, although the fact that this relation was not also present to a greater extent in their White counterparts goes against the hypothesis of the present study and much of the ε4-cognition literature.

Race × APOE ε4 and SPARE-AD (a_3 path)

It was hypothesized that race would moderate the relation of APOE ε4 status to SPARE-AD, such that Whites with APOE ε4 would have higher levels of SPARE-AD than Whites with no APOE ε4 alleles. Likewise, a similar but less pronounced relation was expected among African Americans. It was determined that race had no influence on the relationship between APOE e4 and SPARE-AD in any of the analyses, and thus the results did not confirm the hypothesis. Furthermore, there was no significant effect of ε4 status or race individually on SPARE-AD (a_1 and a_2 paths). Similarly, in the mediation model of an African American only sample, there was no association between ε4 carriership and SPARE-AD (a path) in the exploratory analyses. Currently, no literature exists regarding how the relationship between genetic risk factors and SPARE-AD may vary by racial identity, thus this study was the first to explore this pathway. Not only is there scarcity in the SPARE-AD literature, but racial differences regarding ε4-brain and cognition correlates are extremely understudied and need further examination (Babulal et al., 2019). Despite this, the expectation that race would influence the relation of ε4

carriership on SPARE-AD outcomes stems from the literature detailing ε4-brain outcomes, and some of this literature addresses how this relation may vary by race.

As discussed previously (see *Introduction* and *Prodromal State*), AD-pathophysiology occurs on a cognitive and neuroanatomical continuum, with preclinical, prodromal, and dementia profiles running along the spectrum (Jack et al., 2018). As AD is often preceded by a prodromal state, it has been found that the brain-cognition patterns observed in AD are also present to a lesser extent in the prodromal stage (Albert et al., 2011; Elahi & Miller, 2017; Petersen et al., 2018). Additionally, although neurofibrillary degeneration profiles often align with clinical dementia status, they can precede cognitive impairments, which suggests that some individuals may meet neuropathological criteria without appearing to be in the dementia phase of the AD continuum (Hampel et al., 2008; Hyman et al., 2012). Thus, although a sample may be classified as unimpaired or dementia-free, it may still demonstrate accumulation of cognitive or neuroanatomical factors that map onto the AD-pathophysiological continuum. To this extent, a longitudinal study of 329 dementia-free older adults conducted a significant examination of brain outcomes that investigated how race and the ε4 allele interact to impact neuroanatomical profiles. The study found that African Americans had a two-fold increase in the rate of global Aβ deposition than Whites, and this pattern remained even when adjusting the model for vascular risk factors. However, there was no evidence for a race × APOE interaction on Aβ in the brain (Gottesman et al., 2016). Findings of the current study are similar in that there was also no evidence for race ×APOE ε4 interaction on SPARE-AD outcomes. Unlike the current study, much of the prior literature has focused on the ε4 allele's role in amyloidosis, despite neurodegeneration profiles being

highly predictive of cognitive outcomes and potentially acting as a mediator for the ε4-cognition relation (de la Torre, 2018; De Reuck et al., 2018; Mahley, 1988; Masters et al., 2015; Tanzi, 2012; Wei et al., 2017).

In those studies that did focus on neurodegeneration instead of amyloidosis, the areas of interest revolved around brain structures involved with memory. For instance, Sencakova and colleagues (2001) conducted a cross-sectional study of 54 healthy African Americans and 32 African Americans with AD to examine AD-specific neurodegenerative profiles and found that hippocampal atrophy was a major indicator of AD pathology in African Americans, much like in Whites. Of note, however, is that these studies primarily investigated AD-specific neurodegenerative profiles among older adults and those with prodromal or incident AD. Thus, a middle aged and preclinical sample such as the one in the present study may not reflect the severity of the findings within the aforementioned literature.

Of those studies that have explored within the preclinical realm, one cross-sectional analysis of 985 cognitively normal participants was conducted to determine the presence of amyloidosis and neurodegeneration using structural MRI and PET neuroimaging (Jack et al., 2014). The study found that APOE ε4 carrier status conferred a higher likelihood of amyloidosis, especially with greater age, and those carrying the allele were most frequently found in the A+N+ or A+N- profiles (Jack et al., 2014). A subsequent study expanded on this methodology by incorporating tau-based PET biomarkers to develop A(amyloid) T(tau) N(neurodegeneration) profiles, and similarly found that ε4 carriers were nearly twice as frequent among A+ profiles compared to A- groups (Jack et al., 2017). These findings provide insight into the typical brain profiles of

APOE ε4 carriers, which is still largely based on an increased likelihood of amyloidosis. The neuropathological-centric research framework does not prioritize gene variants such as the ε4 allele, as they only provide information on overall risks for the development of pathologic change and do not measure the presence of Aβ accumulation or identify an individual's place on the AD continuum (Jack et al., 2018; Sperling et al., 2011). Despite the insights of this study, there remains much more exploration, especially as this and most preclinical studies of ε4-brain relations lack sufficient sampling of African American populations. While the ε4 allele explains the process of amyloidosis, it does not explicitly measure neurodegeneration, which further separates the present study from some of the literature, as it is focused on finding the relation between the ε4 allele and AD-specific neurodegeneration while simultaneously considering the role of race.

The lack of representation of African Americans in AD clinical and preclinical cohorts exacerbates the paucity of literature pertaining to AD-specific brain-correlates in African Americans (Morris et al., 2019) and motivated much of the design of the current study. Overall, the early neuropathological signs of AD on neuroimaging are frequently observed in the limbic region and the medial temporal lobe, specifically the parahippocampal gyrus and the hippocampus, which are connected to cognitive domains such as memory and semantic fluency (Risacher et al., 2009; Stark & Stark, 2017; Wang et al., 2015). Atrophy is the AD biomarker that is most strongly linked with cognitive outcomes, and these regions are also affected by atrophy (Jack et al., 2018). Thus, a focus on neurodegeneration and atrophy measures is important to understand the potential mechanisms by which ε4 impacts cognition across diverse groups. Howell and colleagues (2017) conducted a cross-sectional study of 135 older adults (65 African American and

70 White) to examine racial differences of AD biomarkers between African Americans and Whites across AD states. The study found that cognitively normal and MCI participants of both groups had comparable Aβ42, white matter hyperintensities, and hippocampal volumes. However, the same level of lesion volume was associated with a significantly lower mean cognitive score within African Americans than Whites, suggesting that the impact of neuroanatomical insults on cognition may be more pronounced in African Americans, but independent of APOE ε4. This may hint at a rationale for the null findings of the present study, implying that APOE ε4 alone may be an insufficient genetic factor for explaining the AD-pathophysiologic process, especially in African Americans.

The APOE gene has long been considered as a predictor for Alzheimer's disease due to its role in breaking down amyloid-beta; however, only 20-25% of individuals within the dementia population have the APOE risk factor, with some individuals carrying this variant never even developing dementia (van Groen, 2010). Additionally, twin studies have demonstrated discordance in dementia even when each twin has the APOE risk variant (Maloney & Lahiri, 2016), implying that gene-environment interactions or other gene variants may be more effective predictors, especially in African Americans. Therefore, while APOE may still be a useful risk factor for assessing an individual's risk of developing AD, it should be interpreted with caution and in the context of other risk factors. As discussed previously (*Genetic Underpinnings of AD* section), other genes are associated with the progression across the AD-continuum from a physiological and cognitive perspective, such as PSEN, CR1, CLU, and *PICALM*; however, as there over a dozen AD susceptibility genes (Bertram et al., 2007) focusing

on one of these other genes is not the only alternative to probe how gene-brain and gene-cognition relations vary across a diverse sample. Some literature has relied on the use of a genetic risk score for AD, which takes into account multiple genetic risk factors instead of relying solely on APOE or any one gene variant. This approach may be particularly useful in identifying individuals who may be at higher risk for developing Alzheimer's disease but who do not carry the APOE-ε4 allele and can tailor the gene variants to those of the sample being studied. This could further explain the null findings of the present study, as even within the HANDLS sample, a genetic risk score for AD has already been probed (Hossain et al., 2019), and thus may further suggest that the current race ×APOE paradigm may not be sufficient for future studies.

Taken together, there was no race × APOE ε4 interaction on SPARE-AD across any of the analyses of the present study. Although this is the first study to probe this specific interaction, many previous studies suggest that ε4-brain relations in African Americans match the directionality observed in Whites (Jack et al., 2018; Schuff et al., 2008; Sencakova et al., 2001; Vemuri & Jack, 2010; Wang et al., 2015). Thus, it was expected that carriers would have more AD-specific neurodegeneration, with African Americans demonstrating an attenuated relation compared to Whites due to the literature suggesting that African Americans experience less deleterious effects from ε4. A caveat to this is that much of the ε4-brain literature focuses on the amyloid hypothesis, which does not directly map to neurodegeneration. The null findings of this study suggest that the current race × APOE and SPARE-AD paradigm may not be sufficient, setting the stage for future research to employ alternative approaches. It may be beneficial to explore other genes associated with AD progression and use genetic risk scores that consider

multiple genetic risk factors to develop a more comprehensive understanding of gene-brain and gene-cognition relationships in diverse populations.

Race × SPARE-AD and Cognitive Performance (b_2 path)

It was hypothesized that race would moderate the relation of SPARE-AD score to cognitive function such that White participants with greater SPARE-AD would have lower levels of cognitive function than Whites with lower SPARE-AD. A similar, but potentially more pronounced relation was posited among African Americans. In the current analyses, the interaction of race and SPARE-AD did not play a significant role for predicting cognitive performance and did not confirm the hypothesis of the current study. Additionally, there was no significant effect found for the relation of SPARE-AD to cognitive performance in this model (b_1 path). Likewise, in the simple mediation of the exploratory analyses, SPARE-AD was not significantly associated with any cognitive measures (b path) in an African American only sample. The use of SPARE-AD as a neuroanatomical endpoint originally seemed to be an encouraging approach to distinguish patterns of brain atrophy across the cognitive continuum with potentially improved precision than probing regions of interest via simple volumetric measurements (Fan et al., 2008). Although in preclinical samples this technique has shown favorable predictive utility (Davatzikos et al., 2011), little is known regarding the relations of SPARE-AD across different racial backgrounds. The results of the present study suggest that the use of SPARE-AD may not currently be an effective method for detecting preclinical cognitive correlates in different racial groups.

An early consideration for the relationship between race and SPARE-AD was the sparse data available regarding SPARE-AD with participants that were not White. The

present study was not only the first to probe a SPARE-AD × race interaction on cognitive performance, but the only study to extensively discuss and consider the potential sociocultural impact race can have on SPARE-AD outcomes and relationships. To date, no SPARE-AD literature acknowledges the disparities in AD and MCI incidence in the African American population nor does any of the SPARE-AD literature mention the historically mixed findings pertaining to ε4-cognition and ε4-brain outcomes in African Americans. In fact, the vast majority of studies utilizing the SPARE-AD index are being done in samples with 88-94% White participants. Therefore, the application of this measure in a study with 37.9% African American Americans (CVLT sample) and 35.4% African Americans (Semantic Fluency sample) offered a new opportunity in elucidating the impact of race on ε4-cognition outcomes via the SPARE-AD measure as a mediator.

As previously discussed at length (see *Rationale for Race as Moderator and Race and Brain Outcomes*), there is evidence that the brain-correlates in African Americans, like the cognitive-correlates observed throughout the cognitive continuum, match the directionality observed in Whites (Sencakova et al., 2001); however, there also appear to be differences between African American and White individuals in terms of AD-specific neuropathologic differences (Graff-Radford et al., 2016; Wilkins et al., 2006). As a result, thorough measures of neurodegeneration were thought to reveal differential insight in the ε4-brain relation based on the various health factors implicated by race. These differences may in turn provide a rationale for the difference in directionality seen in the Race × APOE ε4 and Cognitive Performance arm of the present study, as well as the null findings regarding Race × SPARE-AD and Cognitive Performance. It has also been proposed that African Americans are more vulnerable to risk factors that aggravate

neurodegeneration, as evidenced by smaller hippocampal volume in those with a familial history of dementia (Howell et al., 2017) and more pronounced cognitive decline for comparable levels of neuroanatomical sequalae (Gottesman et al., 2016; Gu et al., 2015; Howell et al., 2017; Morris et al., 2019). These factors may also suggest that additional adjustment for confounding variables that are implicated with cognitive decline should considered, such as quality of education, diet, and other aspects of cognitive reserve.

The novel aspects of the present study centered on the diversity of the present sample and the fact that race moderation remains to be studied using a robust machine-learning derived neuroimaging biomarker. It was hypothesized that the relationship between race and cognitive decline along the AD-continuum may be stronger in African Americans compared to Whites due to a pathway that is not related to the ε4 genetic risk factor but depends more on the systemic factors that make African Americans more susceptible to neuroanatomical insults. The use of SPARE-AD was going to be an opportunity to probe this hypothesis as it offered a potential explanation as to why African Americans have a higher risk of AD and cognitive decline, despite having a weaker connection to the ε4 genetic risk factor. Despite the promising nature of SPARE-AD as a mediator for a diverse sample, a potential explanation for its lack of findings in the present study may be in large part due to the basis in which its algorithm was created. The classification method and algorithm utilized for SPARE-AD was built using T_1-weighted structural scans from the ADNI, which may likely impact its transportability to some other datasets.

Due to the generally healthy, predominately White, and highly-educated nature of the ADNI sample population, it may not be relevant to a more diverse population

(Gianattasio et al., 2021). Of note is that comorbidities, SES, stress, and education—factors that systemically disenfranchise marginalized groups—may also affect the association between biomarkers and cognitive decline. Therefore, while ADNI and similar studies are valuable for AD research, their findings should not be assumed to be directly applicable to other populations, much less the classification methods and algorithms that are derived from them. However, the difficulty of ADNI findings to be generalized to other populations may severely limit their applicability, although ultimately the extent of its ecological validity remains unclear.

In brief, probing the race × SPARE-AD interaction on cognitive performance yielded no significant effects across any measures of cognitive performance. It was hypothesized that African Americans may exhibit similar brain and cognitive correlates to Whites but also have AD-specific neuropathological exacerbations that explain the higher prevalence of AD in this population. Some literature has suggested that African Americans with the same degree of neuroanatomical insults experienced a greater decline in cognition than Whites (Howell et al., 2017), although race × brain outcomes remain to be exceedingly understudied (Babulal et al., 2019). The present study aimed to shed light on race's impact on brain-cognition outcomes using SPARE-AD, yet it appears that factors that were not adjusted for in the present study may have affected the association between biomarkers and cognitive decline (e.g., vascular comorbidities and comprehensive factors that encompass different aspects of socioeconomic status).

Lack of Mediation (No Significant ab paths)

The indirect effect in this moderated mediation model refers to the effect of ε4 status on cognitive performance through SPARE-AD, which is moderated by race. It

represents the mediated effect of the ε4-cognition relation through the mediator, but with the additional consideration that the strength or direction of this effect may vary depending on race and was quantified using bootstrapping to allow for estimating the indirect effect and its confidence interval. We expected that a race-moderated ε4-cognition relationship would be partially explained by the influence of the ε4 allele on early aspects of brain atrophy. As the confidence interval included zero across all indirect effects in the moderated mediation, the results did not confirm the hypothesis and suggest that there is not enough evidence to conclude that the mediation effect is statistically significant within this model. Given the sensitivity and specificity of the SPARE-AD measure, it was hypothesized that it would be attuned to the subtle neuroanatomical changes in a preclinical sample to predict potential cognitive deficits (Da et al., 2014; Davatzikos et al., 2011). As mentioned in the previous section, the SPARE-AD index has some limitations within this moderated mediation model, primarily when probing a sample of both African American and White adults.

We further conducted exploratory analyses that investigated whether the relation between APOE ε4 status and cognitive outcomes in a sample consisting only of African American participants was mediated by SPARE-AD, while controlling for age, gender, poverty status, and literacy. The aim was to gain a better understanding of the mediational process in the original models, especially as the African American participants in both the Semantic Fluency and CVLT samples had notably higher percentage of individuals below the 125% poverty status (Table 3 and Table 4). This approach was spurred by the work of Whitfield and colleagues (2008), who questioned the adequacy of using race comparisons alone for understanding the behavioral aspects of

aging in racial and ethnic groups. They argued that the study of older adults within racial and ethnic minority groups should go beyond simple between-group comparisons and employ multiple approaches to advance the science of minority aging. Their work highlighted the limitations of past cross-cultural research and emphasized the need for convergence of research designs, statistical techniques, and measures to yield more robust findings by emphasizing the importance of utilizing both within-group and between-group approaches in studies to allow for direct comparisons and meta-analytic analyses (Whitfield et al., 2008). This also challenges the notion that White participants should always be the default contrast group and encourages researchers to ask different questions to advance the understanding of ethnicity and aging. The exploratory analyses of the current study were conducted to observe the simple mediation model on African American participants, which indirectly evaluated the suitability of SPARE-AD as a mediator for cognitive outcomes in African American participants; however, these analyses yielded null findings across all outcomes.

Although this is the first study to probe this specific SPARE-AD mediation model, the literature suggests that ε4 correlates with neurodegeneration in a dose dependent manner (Chételat & Fouquet, 2013) and neurodegeneration is often associated with cognitive impairment and AD-pathophysiology (Talwar et al., 2021; Vemuri & Jack, 2010; Wang et al., 2015), which further supports the rationale for the proposed hypothesis. Despite this, the neurodegeneration patterns found in the present study seemed subtle for this population, suggesting either being unable to fully pick-up the impact of atrophy on cognitive status or perhaps a lack of atrophy due to the young mean age of this sample. In fact, the mean SPARE-AD scores of the present study (Table 1) are

not only markedly more negative (i.e., demonstrating less AD-pathology) compared to either AD or MCI groups in some the SPARE-AD literature, but significantly more negative than even the Cognitively Normal (CN) groups in the SPARE-AD literature (Davatzikos et al., 2011b). Of note, the mean age of the CN group in that study was 75.2±5.40, which is significantly older than the mean age of the present study with the mean age being in the 50s. This provides a more obvious explanation to the lack of mediation effects across all analyses of the present study: the participants as a whole are not exhibiting enough neuroanatomical impairment from a SPARE-AD perspective to demonstrate significant results. Therefore, instead of SPARE-AD, which is designed to measure substantial neurodegeneration similar to Alzheimer's disease, it seems possible that a more refined SPARE algorithm focusing on the subtleties of early cognitive impairments may be developed (Clark et al., 2019; Toledo et al., 2015). This should be considered given the fact that individuals with high WMH burden have higher SPARE-AD values suggesting that this atrophy might not be specific for Alzheimer's disease and might be present in other types of dementia as well (Toledo et al., 2015). Additionally, SPARE-AD could potentially be further disentangled and tailored to increase its sensitivity and correlation to the ε4 allele (Hwang et al., 2022). These alterations to the basic SPARE-AD index suggests that with further refinement it could be altered to increase its correlation to both cognitive changes and allelic specificity; yet at its current state may not be appropriate for this sample.

Furthermore, the use of only CVLT (total, short, and long free recall) and Semantic Fluency in the present study may have been too restrictive for probing the influence of SPARE-AD on ε4-cognition relations. For example, a recent study probed

the role of processing speed on everyday functioning and neuroanatomical endpoints by using a variety of neuropsychological tests, which included semantic fluency (animals), to generate a composite score for processing speed (Wadley et al., 2021). This study found that the processing speed composite score was negatively associated with the SPARE-AD score, suggesting that slower processing speed is associated with a higher level of AD-like whole brain neuroanatomical patterns. Interestingly, the presence of ε4, SNP score, volume of white matter hyperintensities, and volume of the left hippocampus were not found to be related to cognitive processing speed when considered individually (Wadley et al., 2021). This study also found that patterns of cerebral atrophy consistent with AD (higher SPARE-AD scores) were associated with worse driving skills, IADL dysfunction, and poorer everyday mobility. The use of composite cognitive scores was briefly considered for the present study, however the limitations of such an approach outweigh the benefits. Sufficient evidence exists to suggest that continuous measures of cognitive function provide a more robust method to examine e4-cogniton e4-brain relations; however, this still raises the question that the limited cognitive measures used in the present study may have restricted the observed impact of SPARE-AD on cognition.

Of additional note, the sample used by Wadley and colleagues (2021) was significantly older than the current study and thus incident AD and MCI were more likely to influence these outcomes. The age of samples found through the literature are especially relevant given the long and gradual accumulation of prodromal AD-progression. This buildup of AD pathology is present even before the obvious symptoms emerge, which implies that even individuals in their late 50s may already fall into the prodromal AD pre-dementia stage. This is why recent research has shifted to studying the

effects of APOE gene on cognitive abilities in middle-aged individuals (between 30-50 years) to understand the impact of genetics on the AD-continuum in the absence of prodromal symptoms or incident AD (O'Donoghue et al., 2018). Middle-aged cohorts are also more likely to bypass the potentially antagonistic pleiotropic effects of ε4 in early life. It has also been suggested that without very large samples, the inclusion of participants with a wide age range is unlikely to provide clear results (O'Donoghue et al., 2018).

This is a clear strength of the middle-aged cohort of the current study, (mean age = 53.4 in the semantic fluency sample and mean age = 53 in the CVLT sample). A potential pitfall, however, could be that the current range of the sample is not quite as narrow (approximately 35-72 years). This becomes especially important when taking into account racial disparities across age groups where African Americans that reach older adulthood may have had certain characteristics or contextual factors that conferred cognitive benefits along with increased lifespan (Brewster et al., 2019; Weuve et al., 2018). This consideration further highlights the novelty of this mediation model which is compounded by the diversity of the sample in the primary analyses as well as the exploratory analyses of the African American only sub-sample.

In brief, the indirect effect in this moderated mediation and the exploratory analyses found that SPARE-AD did not contribute to the ε4-cognition relation across any cognitive measures in the present study. Given how strongly neurodegeneration correlates to cognitive outcomes and AD-pathophysiology (Jack et al., 2018; Talwar et al., 2021; Vemuri & Jack, 2010; Wang et al., 2015), it was hypothesized that AD-specific neurodegeneration would be a key factor in explaining the mechanism in which ε4 affects

cognition. The null findings suggest that SPARE-AD does not clarify the underling pathway between ε4 carriership and cognitive performance in this study. A likely contributing factor to this could be that the age of participants in the present study precludes the presence of significant AD-specific neurodegeneration, and thus SPARE-AD cannot accurately mediate the ε4-cognition relation. The fact that this model did not demonstrate significant findings is likely due to some of these aforementioned methodological weaknesses, which segues into the current limitations and future directions of the present study.

Strengths, Limitations, and Future Directions

In terms of strength, this study used a unique methodological approach to investigate ε4-cognition and ε4-brain relations within a diverse sample while still paying specific consideration to marginalized groups. It used an ample sample of participants with novel imaging data to ask tailored questions focusing on AD-related outcomes. Additionally, the study was the first to use the specific moderated mediation models in the literature to simultaneously probe race's influence of ε4-cognition and ε4-brain outcomes. As discussed previously, there are countless cultural, geographic, ancestral, and socioeconomic factors that disproportionately affect African Americans and other marginalized groups such as: limited access to quality education, neighborhood conditions, and high levels of lifetime stress. Investigating race as a moderator aimed to indirectly address these risk factors that impact cognitive performance and AD-specific neurodegeneration.

Although the SPARE-AD index has demonstrated to be a more specific and sensitive measure for AD identification than an ROI (Davatzikos et al., 2009; Fan et al.,

2008), its use of machine learning methodologies depends on an underlying pattern to derive its classification system (Kumar et al., 2021). This belies a potentially major limitation for the current study's use of the SPARE-AD index: a reliance on the classification method derived from the ADNI sample to build its algorithm (Davatzikos et al., 2009; Fan et al., 2008). The subjects recruited for ADNI may not be representative of the general population, as they tend to have higher levels of education, are predominately White, and have a higher proportion of APOE ε4 carriers in MCI and AD groups, which is typical for subjects recruited for clinical trials (Petersen et al., 2010) but not necessarily community populations or those found within HANDLS.

At face value this may not seem problematic given the sophistication of machine-learning models, yet some studies suggest that it may be problematic to draw conclusions based on racial comparisons derived from datasets with racial differences in enrollment strategies (Gleason et al., 2019). The bias introduced by enrollment strategies can ultimately result in a form of selection bias-by-design and be considerably difficult to overcome even with the use of advanced algorithms because it limits the transportability of such an approach (Bareinboim & Pearl, 2013; Gleason et al., 2019). Given the overwhelming lack of African American participants in the ADNI study, the transportability and overall generalizability of findings derived from it may be difficult to accurately apply to other populations or models (Gianattasio et al., 2021) and thus the SPARE-AD index may also be impacted by this bias.

There is no doubt that the inclusion of underrepresented groups is exceedingly imperative in preclinical studies for developing proper ecological validity and generalizability of findings for studies relating to AD progression, risk factors, and

mechanisms (Brewster et al., 2019; Manly et al., 2021). Therefore, it is relevant to address that the underlying classification used to build the SPARE-AD index may obscure accurate findings or conceptualizations regarding AD outcomes and factors among both Whites and African Americans. This highlights the need to either disentangle and recalibrate the SPARE-AD algorithm for a more diverse population or return to using ROIs as a neuroanatomical factor for ε4-cognition and ε4-brain relations.

Furthermore, it is important to note that the age of the current sample may also impact the utility of the SPARE-AD measure, and perhaps future directions could incorporate age as an additional moderator. Much of the literature in even preclinical samples are comprised of older adults only, which may create confounds in the ε4-cognition association due to the subtle impacts of accumulating AD-pathology, and thus may not accurately represent true preclinical states (O'Donoghue et al., 2018; Wisdom et al., 2011). This is exacerbated by the fact that the prevalence of vascular pathology may be higher in older samples, which could potentially obscure the relationship between ε4 and cognitive performance in preclinical samples (Iadecola, 2013). In fact, in the current study a relatively low percentage of participants had diagnosed hypertension or high cholesterol (Table 1). Thus, SPARE-AD may not be refined enough to measure AD-specific atrophy patterns in the current middle-aged cohort, as they may be too young and relatively healthy to notice stark contrasts in AD-neuropathology. Ultimately, future studies should seek to use machine learning methodologies from a more diverse underlying sample or, in absence of such approaches, even return to using simple volumetric or ROI neuroanatomical outcomes.

Another limitation that arose was the impact of ε4 dosage on the ε4-cognition relationship, particularly in the context of race. The primarily heterozygous ε4 samples suggest that oversampling for homozygous carriers would be more beneficial for understanding the ε4-cognition and ε4-brain pathways. However, some literature suggests that a genetic risk score for AD, which accounts for multiple genetic risk factors, may provide more accurate predictions relying on ε4 alone. This is because AD is a complex disease with multiple genetic and environmental risk factors, and the use of a single gene variant may not provide a comprehensive understanding of an individual's risk for AD. Therefore, future studies could benefit from utilizing a genetic risk score for AD to provide a more comprehensive understanding of cognitive health in diverse populations.

Future avenues could also utilize more neuropsychological tests and cognitive outcomes to explore domains of cognition impacted by atrophy that may not necessarily by AD-specific. Additionally, as many individuals with AD may also experience co-morbid atrophy or lesions as a result of cardiovascular insults as the progress across the AD-pathophysiological continuum, it may be prudent to explore ε4-cognition relations to domains that are not as commonly explored in relation to AD (e.g., attention). This also suggests incorporating cardiovascular risk factors or measures of racial discrimination/stress in future studies to further probe the impact of systemic factors within this current moderated mediation model. Another limitation is that this study was cross-sectional and did not investigate changes in SPARE-AD or the impact of ε4 carriership and cognitive function over time. Future research should use longitudinal studies to examine this. Ultimately, this study sets the stage for more questions of this

caliber to be asked and to build upon the sparce and often mixed literature within this arena.

Study Implications

Based on the current findings and the state of the literature, it is clear that investigating the relationship between the APOE ε4 allele and cognitive outcomes in preclinical AD among diverse populations is a worthwhile pursuit. Yet, while it is certainly worthwhile to continue investigating the potential neuroanatomical pathways through which the APOE ε4 allele impacts cognitive trajectories, it should be noted that the use of SPARE-AD as a measure of neurodegeneration is not without limitations in diverse samples. In fact, the present findings may suggest that an alternative neuroanatomical pathway may be more appropriate when probing the impact of racial identity on ε4-cognition relations among middle-aged individuals. Although SPARE-AD may be a useful measure in some contexts, it may not provide a comprehensive picture of the neuroanatomical mechanisms that underlie the relationship between APOE ε4 and preclinical cognitive outcomes, particularly in middle-aged African American samples. Thus, future investigations in this area should consider using multiple neuroanatomical measures to gain a more comprehensive understanding of the mechanisms underlying the ε4-cognition relationship. Additionally, future research should continue to explore potential racial disparities in the ε4-cognition relation, as previous investigations have shown that the impact of the ε4 allele on cognitive outcomes may vary across racial and ethnic groups (Fillenbaum et al., 2001; Maestre et al., 1995; Mayeux et al., 1993; Rajabli et al., 2018; Ren et al., 2021; Sawyer et al., 2009; Tang et al., 1996; Weuve et al., 2018). Understanding these disparities is essential for developing effective interventions and

treatments for individuals at risk for Alzheimer's disease, regardless of their racial or ethnic background. As discussed throughout the limitations section, most prior literature has primarily focused on studies conducted in predominantly White samples, which may not necessarily generalize to other racial and ethnic groups. Thus, further research is needed to better understand the potential impact of race on the APOE ε4-cognition relation, and whether there may be differences in the neurobiological mechanisms underlying this relationship in different racial and ethnic groups. It is crucial to consider such factors in future research, as well as to strive for more diversity in study populations in order to improve the generalizability of findings and better understand the complex interactions between APOE ε4, race, and cognitive function.

Despite some mixed results, in terms of translational significance, continued investigation in this area has the potential to further our understanding of the early stages of the AD continuum and could ultimately lead to the development of more effective prevention and treatment strategies. Overall, several studies have found that individuals with the ε4 allele exhibit steeper declines in cognitive function over time and are at an increased risk for progressing through the AD-pathophysiological continuum. At the same time, it is important to note that the impact of the ε4 allele on cognition is likely complex and multifaceted, potentially involving amyloidosis, other neuroanatomical mechanisms, influenced by race, and may be exacerbated by cardiometabolic factors. Even the very study of the ε4 allele is not a monolith, and ancestral genetic data should be considered to further disentangle the ε4-cognition and ε4-brain relations within the literature as a whole (Rajabli et al., 2018). In the absence of this kind of data, the consideration of shifting towards a more holistic genetic risk score, instead of singular

allele relations may be another acceptable alternative (Hossain et al., 2019). Future studies should explore these potential mechanisms more deeply and may consider using multiple cognitive measures that are sensitive to subtle variations in cognition and can capture domain-specific changes over time.

Conclusions

The findings of the current study suggest that the relation of APOE ε4 status to cognitive performance may, in some instances, vary by race. The current findings revealed unexpected patterns, such that White ε4 carriers performed better than non-carriers on semantic fluency, contrary to the higher risk for cognitive decline typically associated with ε4 alleles. On the other hand, African American carriers of ε4 performed worse than non-carriers on CVLT short free-recall, aligning with the general trend of APOE ε4-cognition relationships despite some literature suggesting that this trend is not seen (or is at least weaker) in African Americans. However, these associations were not mediated by SPARE-AD. From this study, we have learned that the relationship between APOE ε4 status, race, and cognitive performance is complex and requires a careful exploration of the potential pitfalls of investigating the ε4-brain and ε4-cognition relations in middle-aged samples.

Future studies should explore alternative variables and methodologies to elucidate the complex nature of genetics and its impact on early cognitive and brain outcomes that identify risk for AD. Specifically, investigating additional cognitive measures (i.e., beyond memory and semantic fluency), considering other neuroanatomical mechanisms, different genetic risk factors, and examining cardiometabolic factors could provide a more comprehensive understanding of the ε4-cognition relationship. It is also crucial to

further expand research to include diverse populations and collect both ancestral genetic data and biopsychosocial and socioeconomic risk exposures that disproportionately affect African Americans and other marginalized groups to disentangle the mixed ε4-cognition and ε4-brain relations within the broader literature. Considering a more holistic genetic risk score, rather than focusing solely on individual alleles, could be a valuable alternative approach. Addressing these gaps in the present study could further advance the current conceptualization of the AD-pathophysiological continuum and create an avenue to potentially develop more effective strategies for the prevention and treatment of cognitive decline associated with AD.

Appendix A: All Tables

TABLE 1. SAMPLE CHARACTERISTICS	*Semantic Fluency Sample*				*CVLT Sample*			
	Mean	SD	Percent	Range	Mean	SD	Percent	Range
Age (years)	53.40	9.26		35-72	53.03	9.14		35-72
% female			57.0				55.7	
% African American			35.4				37.9	
% below 125% poverty line			31.0				34.3	
% current alcohol drinker			64.1				64.3	
% HTN			35.7				35.3	
% prescribed cholesterol medicine			13.9				13.4	
% Any APOE ε4 allele			26.6				28.6	
Years of Education	12.3	2.71		2-20	12.2	2.83		2-20
SPARE-AD Score	-2.59	.74		-5.27- -0.74	-2.57	.74		-5.27- -0.74
Scores of neuropsychological tests								
WRAT total score	44.04	6.89		21-55	43.59	7.06		21-55
CVLT list A total					25.11	6.64		7-39
CVLT short delay					7.48	3.20		2-15
CVLT long delay					7.79	2.99		1-15
Semantic fluency (animals)	19.72	4.72		10-32				
	***N* = 158**				***N* = 140**			

Table 2. Correlation matrix of study variables

Variables	*apoE4carriership*	*Race*	*Age*	*Sex*	*Poverty status*	*Literacy (WRAT Total score)*	*SPAREAD*	*CVLT Total correct A*	*CVLT A Short-Delay Free Recall*	*CVLT Long-Delay Free Recall*	*Animal fluency total words*
apoE4 carriership	1	.290**	-0.015	0.077	0.066	-0.010	0.089	-0.078	-.184*	-0.160	0.113
Race	.290**	1	-.169*	-0.026	.217**	-.329**	0.116	-.232**	-.246**	-.215*	-0.085
Age	-0.015	-.169*	1	-0.020	-.224**	0.096	.209**	-0.101	-.178*	-0.161	-0.064
Sex	0.077	-0.026	-0.020	1	-0.136	0.022	-.188*	-0.094	-0.161	-.209*	0.034
Poverty status	0.066	.217**	-.224**	-0.136	1	-.226**	0.114	-0.110	-0.132	-0.072	-.163*
Literacy (WRAT Total score)	-0.010	-.329**	0.096	0.022	-.226**	1	-0.102	.412**	.345**	.331**	.261**
SPAREAD	0.089	0.116	.209**	-.188*	0.114	-0.102	1	-0.076	-0.121	-0.066	-0.125
CVLT Total correct A	-0.078	-.232**	-0.101	-0.094	-0.110	.412**	-0.076	1	.774**	.750**	.407**
CVLT A Short-Delay Free Recall	-.184*	-.246**	-.178*	-0.161	-0.132	.345**	-0.121	.774**	1	.857**	.378**
CVLT Long-Delay Free Recall	-0.160	-.215*	-0.161	-.209*	-0.072	.331**	-0.066	.750**	.857**	1	.320**
Animal fluency total words	0.113	-0.085	-0.064	0.034	-.163*	.261**	-0.125	.407**	.378**	.320**	1

***. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).*

Directionality Key- Poverty status: below 125% of the federal poverty threshold = 1, income at or above 125% of the poverty threshold = 0; Sex: 0 = female, 1 = male. Race: 0 = White, 1 =African American; APOE ε4 status: 0= Non-carrier 1= Carrier

Table 3. Semantic Fluency Sample Characteristics by Race

	White				African American			
	Mean	SD	Percent	Range	Mean	SD	Percent	Range
Age (years)	54.41	8.98		35-72	51.55	9.56		36-72
% female			55.9				58.9	
% below 125% poverty line			25.5				44.6	
% current alcohol drinker			64.1				64.0	
% HTN			32.7				41.5	
% prescribed cholesterol medicine			16.1				9.8	
% Any APOE ε4 allele			16.7				44.6	
Years of Education	12.3	3.01		2-20	12.4	2.17		3-18
SPARE-AD Score	-2.67	.80		-5.27- -0.74	-2.44	.60		-4.23- -1.10
Scores of neuropsychological tests								
WRAT total score	45.81	6.65		21-55	40.82	6.14		25-53
Semantic fluency (animals)	20.01	5.01		10-32	19.18	4.14		11-29
	***N* = 102**				***N* = 56**			

Table 4. CVLT Sample Characteristics by Race

	White				African American			
	Mean	SD	Percent	Range	Mean	SD	Percent	Range
Age (years)	54.04	8.75		35-72	51.36	9.59		36-72
% female			55.2				56.6	
% below 125% poverty line			26.4				47.2	
% current alcohol drinker			64.6				63.8	
% HTN			32.6				40.0	
% prescribed cholesterol medicine			16.5				8.3	
% Any APOE ε4 allele			17.2				47.17	
Years of Education	12.1	3.19		2-20	12.4	2.22		3-18
SPARE-AD Score	-2.65	.81		-5.27- -0.74	-2.46	.61		-4.23- -1.10
Scores of neuropsychological tests								
WRAT total score	45.24	7.02		21-55	40.87	6.3		25-53
CVLT list A total	26.33	6.74		7-39	23.09	5.99		11-36
CVLT short delay	8.09	3.38		2-15	6.47	2.63		2-12
CVLT long delay	8.32	3.04		2-15	6.91	2.69		1-13
	***N* = 87**				***N* = 53**			

Table 5. Race ×APOE ε4 status on SPARE-AD for Semantic Fluency (a paths)

Variable	Coefficient	Standard Error	t-value	p-value	Lower CI	Upper CI
apoE4 carriership	0.18	0.19	0.96	0.34	-0.19	0.56
Race	0.26	0.16	1.66	0.10	-0.05	0.58
apoE4 carriership x Race	-0.20	0.27	-0.76	0.45	-0.74	0.33
Poverty Status	0.17	0.13	1.31	0.19	-0.09	0.43
WRAT total	-0.01	0.01	-0.64	0.53	-0.02	0.01
Sex	-0.24	0.11	-2.04	0.04*	-0.47	-0.01
Age	0.02	0.01	2.93	0.003*	0.01	0.03

Table 6. Moderated Mediation for Semantic Fluency (c' and b paths)

Variable	Coefficient	Standard Error	t-value	p-value	LLCI	ULCI
apoE4 carriership	3.65	1.19	3.05	0.003*	1.28	6.01
SPAREAD	-0.90	0.57	-1.59	0.113	-2.03	0.22
Race	5.18	3.08	1.68	0.095	-0.91	11.28
apoE4 carriership x Race	-4.05	1.69	-2.39	0.018*	-7.40	-0.71
SPAREAD x Race	1.66	1.18	1.41	0.162	-0.67	3.99
Poverty Status	-1.50	0.83	-1.81	0.072	-3.13	0.14
WRAT total	0.17	0.06	3.04	0.003	0.06	0.28
Sex	-0.17	0.74	-0.23	0.821	-1.64	1.30
Age	-0.07	0.04	-1.70	0.092	-0.15	0.01

Table 7. Conditional direct effects of e4 carriership at values of Race for Semantic Fluency (Animals)

Race	effect	se	t	p	LLCI	ULCI
White	3.65	1.20	3.05	0.003*	1.29	6.01
African American	-0.41	1.20	-0.34	0.736	-2.79	1.97

Table 8. Race ×APOE ε4 status on SPARE-AD for CVLT Total Recall (a paths)

Variable	Coefficient	Standard Error	t-value	p-value	LLCI	ULCI
apoE4Any	0.10	0.21	0.49	0.63	-0.31	0.51
Race	0.19	0.17	1.11	0.27	-0.15	0.52
apoE4 carriership x Race	-0.09	0.29	-0.32	0.75	-0.66	0.47
Poverty Status	0.17	0.14	1.24	0.22	-0.12	0.45
WRAT total	-0.01	0.01	-0.67	0.51	-0.02	0.01
Sex	-0.26	0.13	-2.11	0.04*	-0.51	-0.02
Age	0.02	0.01	2.80	0.01*	0.01	0.03

Table 9. Moderated Mediation for CVLT Total Recall (c' and b paths)

Variable	Coefficient	Standard Error	t-value	p-value	LLCI	ULCI
apoE4 carriership	1.10	1.74	0.63	0.53	-2.34	4.54
SPAREAD	-0.29	0.82	-0.35	0.73	-1.91	1.33
Race	-0.50	4.34	-0.12	0.91	-9.08	8.09
apoE4 carriership x Race	-2.65	2.41	-1.10	0.27	-7.42	2.11
SPAREAD x Race	0.15	1.65	0.09	0.93	-3.12	3.42
Poverty Status	-0.84	1.17	-0.72	0.47	-3.15	1.47
WRAT total	0.35	0.08	4.50	0.00	0.20	0.50
Sex	-1.57	1.08	-1.46	0.15	-3.69	0.56
Age	-0.11	0.06	-1.73	0.09	-0.23	0.02

Table 10. Race ×APOE ε4 status on SPARE-AD for CVLT Short Free Recall (a paths)

Variable	Coefficient	Standard Error	t-value	p-value	LLCI	ULCI
apoE4Any	0.10	0.21	0.49	0.63	-0.31	0.51
Race	0.19	0.17	1.11	0.27	-0.15	0.52
apoE4 carriership x Race	-0.09	0.29	-0.32	0.75	-0.66	0.47
Poverty Status	0.17	0.14	1.24	0.22	-0.12	0.45
WRAT total	-0.01	0.01	-0.67	0.51	-0.02	0.01
Sex	-0.26	0.13	-2.11	0.04*	-0.51	-0.02
Age	0.02	0.01	2.80	0.01*	0.01	0.03

Table 11. Moderated Mediation for CVLT Short Free Recall (c' and b paths)

Variable	Coefficient	SE	t-statistic	p-value	Lower CI	Upper CI
apoE4 carriership	0.47	0.82	0.58	0.56	-1.14	2.08
SPAREAD	-0.19	0.38	-0.48	0.63	-0.95	0.58
Race	-0.41	2.03	-0.20	0.84	-4.44	3.61
apoE4 carriership x Race	-2.46	1.13	-2.18	0.031*	-4.69	-0.22
SPAREAD x Race	-0.15	0.78	-0.19	0.85	-1.68	1.38
Poverty Status	-0.86	0.55	-1.57	0.12	-1.95	0.22
WRAT total	0.13	0.04	3.63	0.0004*	0.06	0.20
Sex	-1.18	0.50	-2.33	0.021*	-2.17	-0.18
Age	-0.08	0.03	-2.84	0.005*	-0.14	-0.03

Table 12. Conditional effects of e4 carriership at values of Race for CVLT Short Free Recall

Race	effect	se	t	p	LLCI	ULCI
White	0.472	0.815	0.579	0.564	-1.140	2.084
African American	-1.987	0.785	-2.531	0.013	-3.540	-0.434

Table 13. Race ×APOE ε4 status on SPARE-AD for CVLT Long Free Recall (a paths)

Variable	Coefficient	Standard Error	t-value	p-value	LLCI	ULCI
apoE4Any	0.10	0.21	0.49	0.63	-0.31	0.51
Race	0.19	0.17	1.11	0.27	-0.15	0.52
apoE4 carriership x Race	-0.09	0.29	-0.32	0.75	-0.66	0.47
Poverty Status	0.17	0.14	1.24	0.22	-0.12	0.45
WRAT total	-0.01	0.01	-0.67	0.51	-0.02	0.01
Sex	-0.26	0.13	-2.11	0.04*	-0.51	-0.02
Age	0.02	0.01	2.80	0.01*	0.01	0.03

Table 14. Moderated Mediation for CVLT Long Free Recall (c' and b paths)

Variable	Coefficient	SE	t-statistic	p-value	Lower CI	Upper CI
apoE4 carriership	0.29	0.76	0.39	0.700	-1.21	1.80
SPAREAD	0.16	0.36	0.44	0.664	-0.55	0.87
Race	-2.93	1.90	-1.54	0.126	-6.69	0.83
apoE4 carriership x Race	-1.93	1.05	-1.83	0.069	-4.02	0.15
SPAREAD x Race	-1.14	0.72	-1.57	0.118	-2.57	0.29
Poverty Status	-0.47	0.51	-0.92	0.358	-1.49	0.54
WRAT total	0.13	0.03	3.80	0.0002*	0.06	0.20
Sex	-1.31	0.47	-2.78	0.0063*	-2.24	-0.38
Age	-0.06	0.03	-2.19	0.030*	-0.11	-0.01

Appendix B: All Figures

Figure 1. Moderated Mediation (Hayes Model 59) Conceptual Diagram

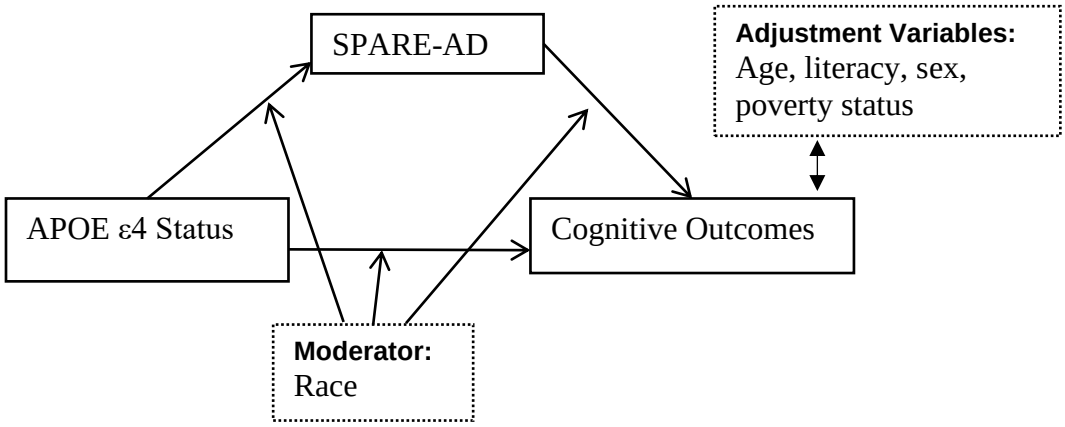


Figure 2. Plot of conditional effects of APOE e4 × Race for Semantic Fluency (Animals)

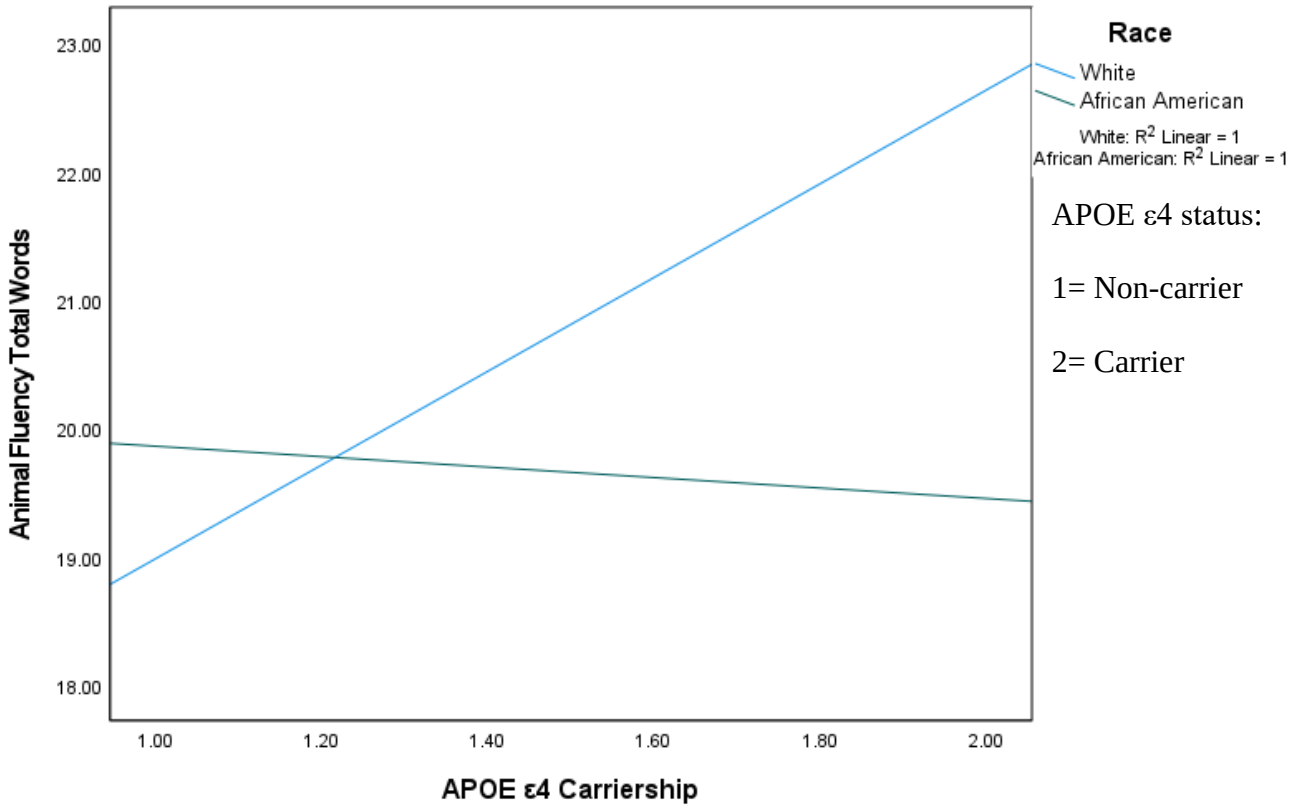


Figure 3. Plot of conditional effects of APOE e4 × Race for CVLT Short Free Recall

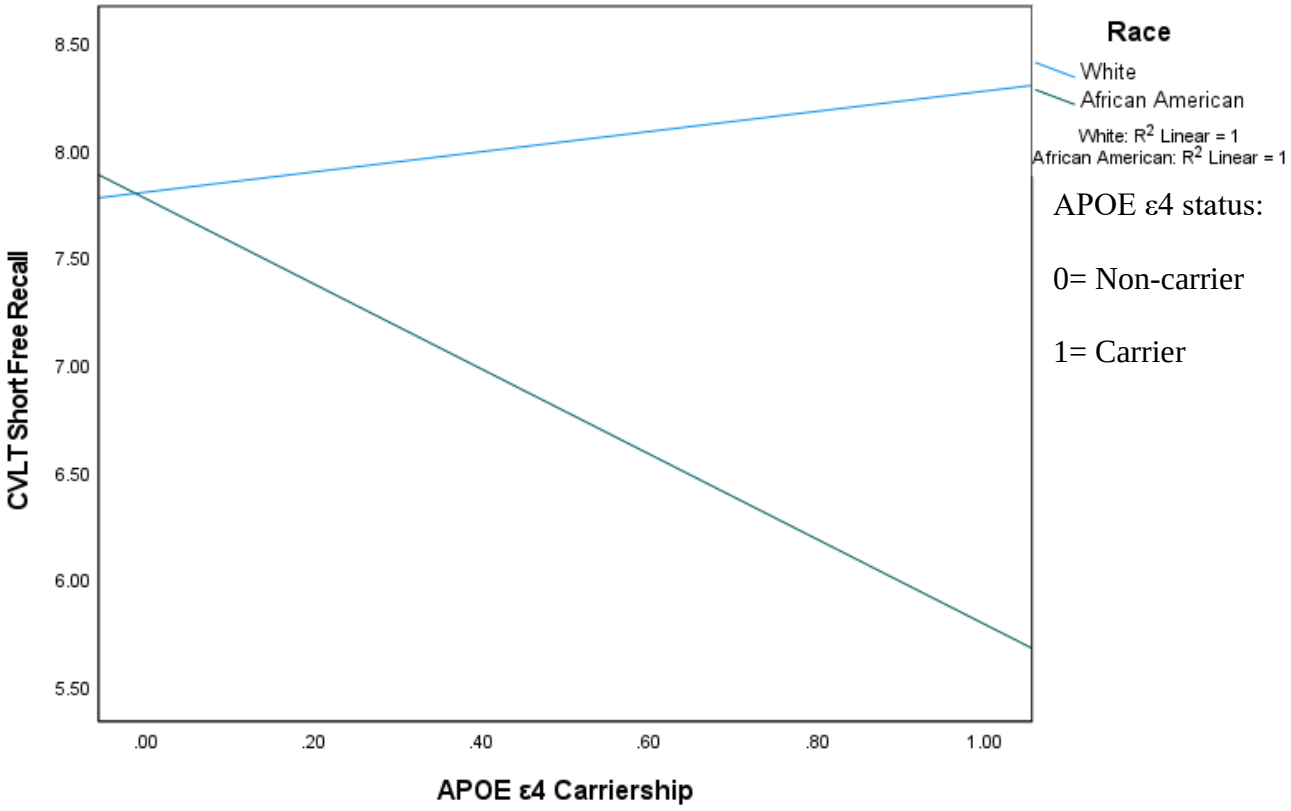
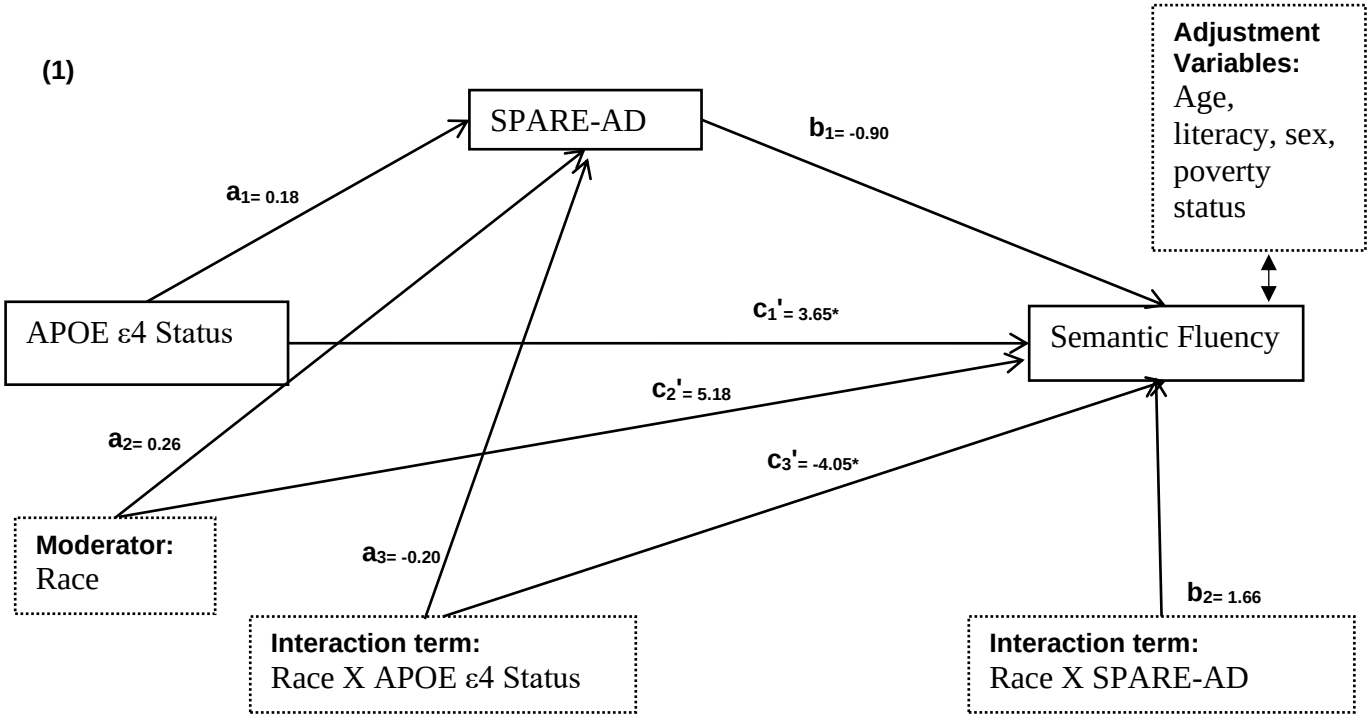
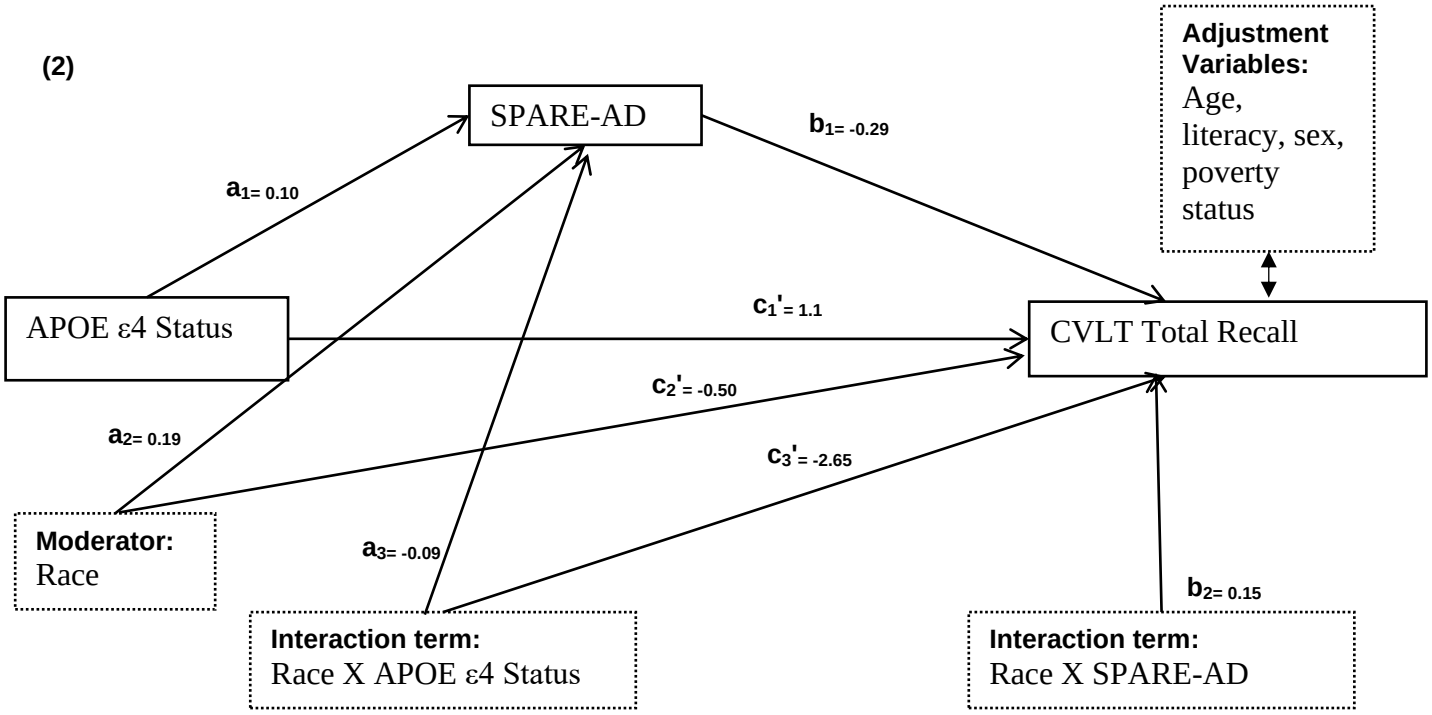
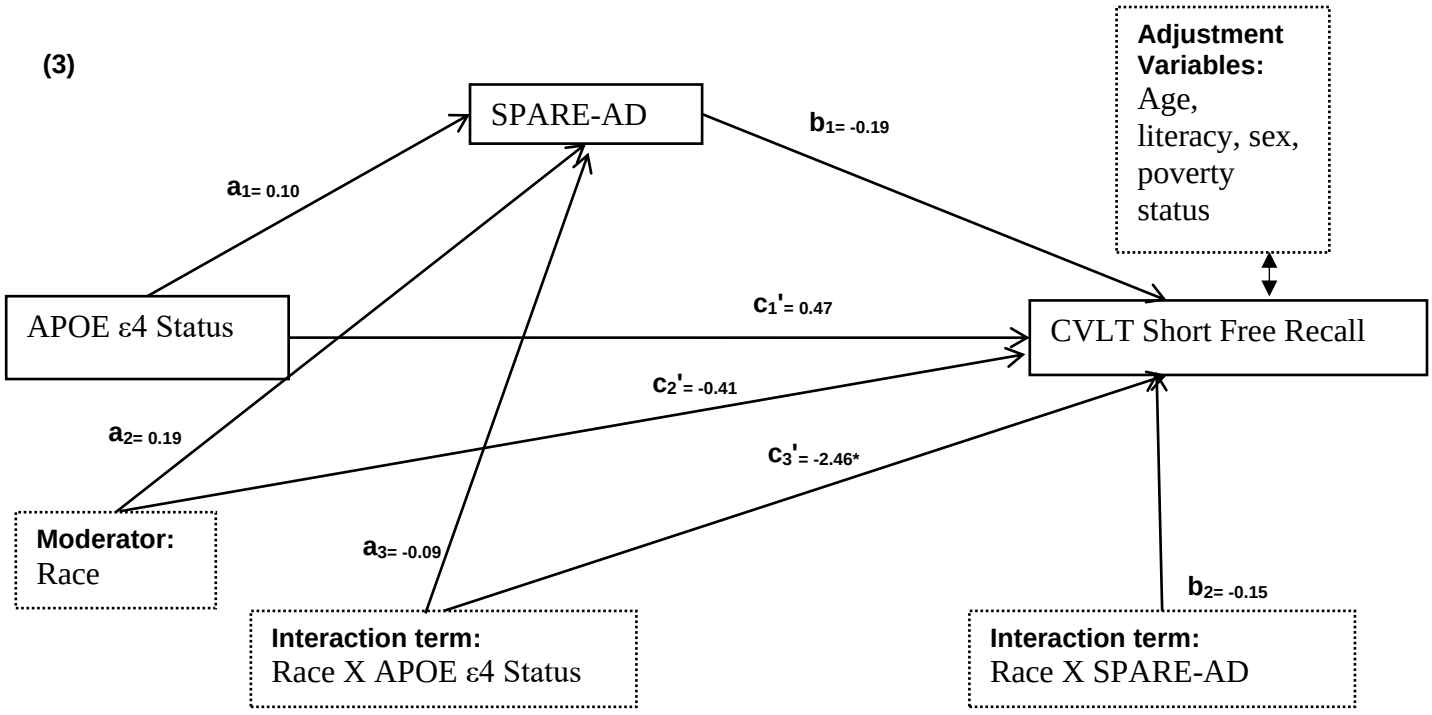
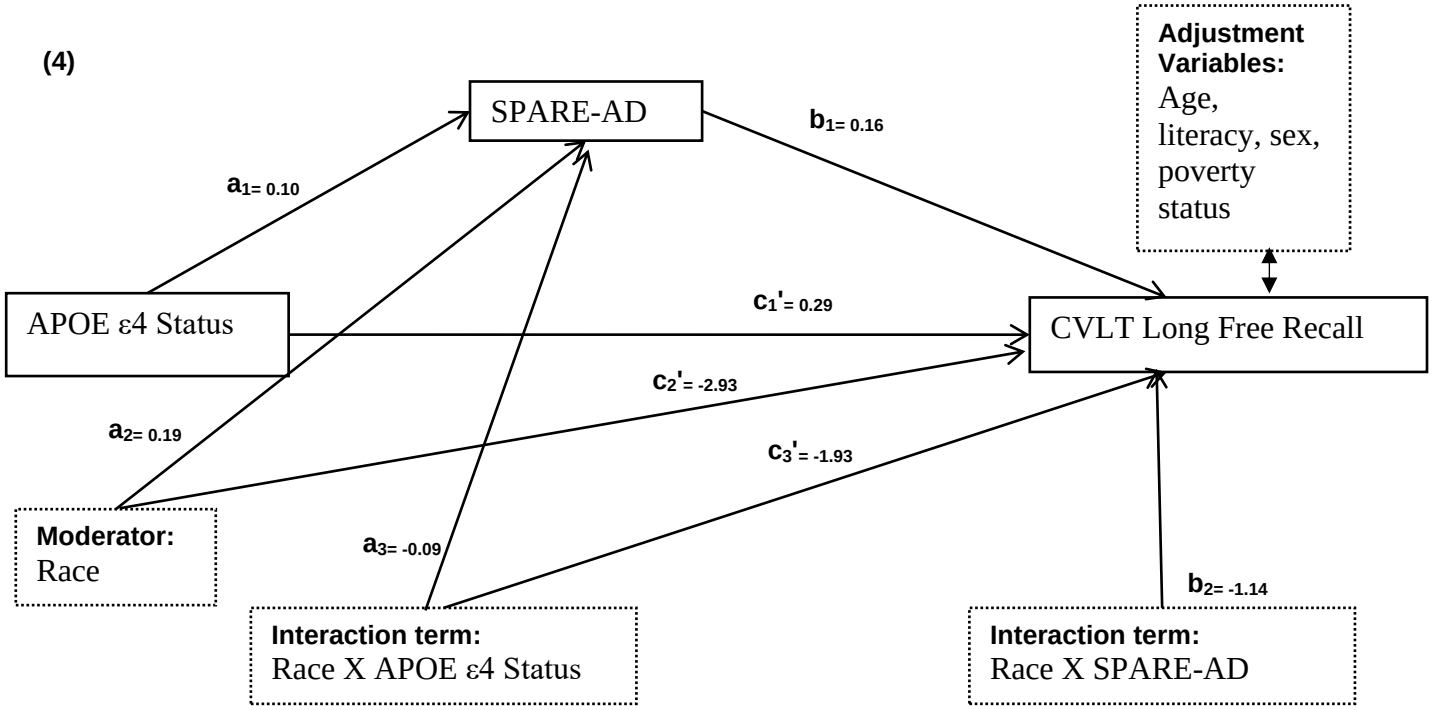


Figure 4. Moderated Mediation (Hayes Model 59) Statistical Diagrams









Statistical path model of Moderated Mediation delineating a paths, b paths, and c paths with coefficients. (1) Model 1: APOE ε4 status, SPARE-AD, Race, and Semantic Fluency. (2) Model 2: APOE ε4 status, SPARE-AD, Race, and California Verbal Learning Test (total). (3) Model 3: APOE ε4 status, SPARE-AD, Race, and CVLT (short free recall). (4) Model 4: APOE ε4 status, SPARE-AD, Race, and CVLT (long free recall). *$p <$ .05; **$p <$ .01

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