Psychology Dissertations   Department of Psychology

12-2020

Decoding the Disparity: An Analysis of the Functional Connectivity Profile of Elderly African Americans with and without Alzheimer's Disease

Maria Misiura

Follow this and additional works at: https://scholarworks.gsu.edu/psych_diss

DECODING THE DISPARITY: AN ANALYSIS OF THE FUNCTIONAL CONNECTIVITY PROFILE

OF ELDERLY AFRICAN AMERICANS WITH AND WITHOUT ALZHEIMER'S DISEASE

by

MARIA MISIURA

Under the Direction of Jessica Turner, PhD

ABSTRACT

African Americans are twice as likely as non-Hispanic Whites to develop Alzheimer's Disease. Current approaches to studying Alzheimer's disease do not include a sufficient minority population needed to understand the nature of this disparity. Evidence from epidemiological and cerebrospinal fluid biomarker studies suggests that African Americans do indeed represent a unique phenotype of Alzheimer's disease, partly driven by an elevated presence of risk factors. These risk factors include, but are not limited to an elevated presence of vascular disease which can manifest in the brain in the form of White Matter Hyperintensities (WMH). Functional magnetic resonance imaging is a method of detecting brain activity, and has been used to detect neurological changes within Alzheimer's Disease in the form of functional connectivity (FC). FC is a measure of the correlation of activity between brain regions. In our first aim, we examined connectivity between a well-studied network, the default mode network and how race modifies the relationship between AD biomarkers and connectivity, and whether WMH in this network accounts for these racial differences. We found that race does modify the relationship between

CSF t-Tau, Aβ42, and cognitive performance between the midline core and dorsomedial subsystems, but that WMH did not account for these differences. In our second aim, we analyzed connectivity between regions not typically associated with AD including the anterior putamen, pre and post central gyri, and superior and middle frontal gyri. We found that, independent of race, anterior putamen to pre and post central gyri increased as CSF Aβ42 decreased, but the connectivity decreased as regional WMH volume increased. Within African Americans, connectivity between the middle and superior frontal connectivity decreased as CSF Aβ42 decreased, and as regional WMH volume increased. This work further characterizes the AA dementia profile, and provides novel regions of exploration that may be affected by AD. Furthermore, we provide neurological support for the claim that in studies of individuals with Alzheimer's disease, race should be considered as an important factor of interest in analyses.

INDEX WORDS: Alzheimer's Disease, Functional neuroimaging, Disparities, Magnetic resonance imaging, cerebellum, basal ganglia, Default Mode Network

DECODING THE DISPARITY: AN ANALYSIS OF THE FUNCTIONAL CONNECTIVITY PROFILE

OF ELDERLY AFRICAN AMERICANS WITH AND WITHOUT ALZHEIMER'S DISEASE

by

MARIA MISIURA

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2020

DECODING THE DISPARITY: AN ANALYSIS OF THE FUNCTIONAL CONNECTIVITY PROFILE

OF ELDERLY AFRICAN AMERICANS WITH AND WITHOUT ALZHEIMER'S DISEASE

by

MARIA MISIURA

Committee Chair:　Jessica Turner

Committee:　William Hu

Bruce Crosson

Tricia King

Electronic Version Approved:

Office of Graduate Studies

College of Arts and Sciences

Georgia State University

December 2020

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

AA= African American

NHW = Non-Hispanic White

AD = Alzheimer's Disease

MCI = Mild cognitive impairment

NC = Normal cognition

MRI = Magnetic resonance imaging

rsfMRI = resting state functional MRI

CSF = Cerebrospinal fluid

WMH = White matter hyperintensities

APu= Anterior Putamen

1 INTRODUCTION

1.1 Purpose of the Study

African Americans are twice as likely as Caucasians to develop Alzheimer's disease (AD) in their lifetime[1]. While hypotheses exist to explain this disparity, there is no known mechanism that fully accounts for it[2]. This lack of knowledge may be attributable to the fact that AD studies typically contain data collected from upper-middle class NHWs (Non-Hispanic Whites) with lifestyle and genetic backgrounds dissimilar to those of African Americans (AAs)[3]. In order to determine the nature of the differences between Caucasians and African Americans with dementia, we must create models that consider the multifaceted concept of race.

One method of modeling neurological changes in dementia is magnetic resonance imaging (MRI)[4]. Functional neuroimaging (fMRI) can identify changes in brain activity that supplement current AD models[5]. Disease related fMRI changes correlate with AD biomarkers including tau deposition[6], amyloid levels[7], brain atrophy[8], and cognitive performance[9]. The proposed study seeks to identify the unique characteristics of the functional imaging profile of African Americans and determine whether ischemic neurological damages in the form of white matter hyperintensities account for any observed disparities.

1.2 A Short Discussion of Race

Before delving into a discussion of the African American phenotype in the context of Alzheimer's Disease, we must first operationalize the concept of race, and how we propose to study it in this body of work. For the purposes of this study, race is a self-reported measure of belonging to a specific ethno-cultural group, in this case either NHW or African American. Although it may seem to be more biologically viable to include only genetic information to determine race, it would exclude relevant lifestyle and cultural factors linked to Alzheimer's disease such as diet, activity levels, and access to healthcare[10–13]. To understand the nature of racial disparities in dementia we will include race as a

variable in our models, and then unpack factors under the umbrella of race such as genetic risk factors, comorbidities, and socio-economic status (SES) to determine the extent to which these factors account for that variability attributed to race.

1.3 Alzheimer's Disease & Health Disparities

Over 5 million Americans currently live with Alzheimer's disease. It is the sixth leading cause of death in individuals over 65[1]. Individuals with Alzheimer's disease will eventually succumb to its effects, but usually not without a gradual decline in daily function. This places a tremendous burden not only on the individuals with AD, but caregivers and health professionals that must provide support for patients during the diseased period of their lives[14]. Despite these facts, it remains as the only disease within the top 10 leading causes of death to have no concrete method to slow, prevent or, cure the disease[1].

1.3.1 Racial disparities in AD

African Americans are twice as likely to develop AD within their lifetime as are NHWs [2]. Additionally, unique ethnoracial AD profiles have been identified for CSF [2,15], blood proteomic[16], genetic[17], and lifestyle risk factors[18]. However, the overwhelming majority of data used to create diagnostic and progression models of AD are from NHW populations[19]. Recruitment and study participation bias likely results from an interplay between convenient sampling[20], and a lack of active networking with diverse populations that may be less likely to seek healthcare at early stages of AD[21], and exhibit more mistrust towards the scientific and medical community[22]. Analyses that explicitly consider race as a variable of interest may not only enable us to uncover the nature of dementia disparities, but indicate to the populations of interest that everyone's unique life experiences and circumstances are valued and important to the scientific community, which could increase research participation of minority groups[23].

1.4   Etiology and Clinical Diagnosis of Alzheimer's disease

While we do not fully understand the causes of and risk factors for AD, the disease pathology is fairly well defined. Alzheimer's disease is characterized by the presence of two cellular abnormalities, amyloid beta plaques, and neurofibrillary (tau) tangles[24]. A definitive diagnosis of AD can only be given after autopsy of the brain[25]. The presence of neuro-fibrillary tau tangles (NFTs) and Amyloid-beta ($A\beta_{42}$) plaques serves the basis for a post mortem diagnosis of AD, but this diagnosis is obviously not relevant for those living with AD. In the clinic, AD dementia is diagnosed using a multi-faceted approach. A diagnosis of Alzheimer's disease usually comes after a consensus among imaging results, cognitive testing, clinical interviews, and, rarely, cerebral spinal fluid biomarkers (tau and $A\beta_{42}$)[26–28].

Tau and $A\beta_{42}$ can be detected in cerebrospinal fluid (CSF), and can aid in the diagnosis of AD, in that if they are present at pathological levels it would support a diagnosis of AD dementia versus another type of dementia[29–31]. Accumulation of $A\beta_{42}$ is normal in the aging brain, but the molecular composition of plaques in AD is unique[24]. The *Amyloid hypothesis* implicates the accumulation of $A\beta_{42}$ as the impetus for AD[32]: i.e., $A\beta_{42}$ plaques accumulate, which then starts a host of cellular inflammatory responses that lead to NFTs, which then leads to neuronal degradation and atrophy[33]. Although it may seem that the presence of $A\beta_{42}$ is pathogenic, we do not know the mechanism by which it is toxic[34]. Despite its widespread acceptance over the last decade, many clinical trials that decrease $A\beta_{42}$ accumulation have failed, discrediting the amyloid hypothesis[32]. While the proposed study does not directly probe the cellular interactions of $A\beta_{42}$, better characterizing the diverse population of individuals with AD may enable researchers to identify similarities in brain pathology that can aid in the refinement of the amyloid hypothesis.

Despite the unanswered questions about $A\beta_{42}$ toxicity, there is much evidence that tau accumulation and migration across the brain has deleterious effects[35]. In its normal state, tau is a microtubule-associated protein whose function is to stabilize microtubules that maintain cell polarity and axonal transport[36]. In AD, tau is typically hyperphosphorylated, which may block necessary microtubule binding sites[36]. When tau is present, but does not serve to stabilize microtubules, the microtubules

disassemble, and tau accumulates in paired helical filaments, forming the classic neurofibrillary tangles (NFTs)[36]. Without the microtubule structure, axonal transport ceases, and the neuron eventually dies. Increased tau levels are detectable in the CSF, and CSF t-Tau serves as a better marker of disease progression than $A\beta_{42}$, as it more closely correlates with cognition[31,37,38].

From a cognitive standpoint, memory impairment is the hallmark cognitive sign of Alzheimer's disease, and is typically correlated with CSF biomarkers of AD and hippocampal atrophy[39,40]. Short term memory deficits are commonly reported in individuals that receive a diagnosis of Alzheimer's Disease. In clinical diagnosis, memory complaints that impair with daily function are often sufficient to receive a diagnosis of AD[40]. However, an individual can present with a mixed cognitive profile, with visuospatial and executive function deficits as opposed to only memory complaints[25–27]. In fact, African Americans are more likely to exhibit non-amnestic cognitive profiles than NHWs[42].

Much of the diagnostic process of AD involves ruling out other causes of dementia including stroke, vascular dementia, Parkinson's disease, geriatric depression, etc. While CSF measures and PET images have greater specificity for AD, combined with magnetic resonance imaging (MRI), they are much more powerful, and MRI has been cited as more stable indicator of neuronal loss than CSF markers[44].

1.4.1 *Racial Disparities in diagnostic models of AD*

In multiple cohorts, African Americans have lower CSF total tau than NHWs[15,45] despite similar levels of $A\beta_{42}$ and similar cognitive function. This may suggest that African Americans exhibit pathological processes after amyloid deposition distinct from NHWs. Additional considerations include genetic risk factors unique to race. APOE e4 and the ABCA7 alleles occur at increased rates in AAs, and confer different risks across races[46]. ABCA7 confers a greater risk for AD in AAs, and is present at higher rates in this population[17,47]. Presence of the APOE e4 allele has differential effects on functional connectivity according to race[48]. We will carefully consider these risk genes in our analyses to determine whether their presence explains the racial differences we may observe in connectivity to biomarker

relationships. Furthering our understanding of the observed differential tau and genetic burden in the context of additional AD biomarkers may broaden our understanding of Alzheimer's disease, and allow current models to be more generalizable.

In general, African Americans may exhibit a distinct cognitive profile in the presence of AD. African Americans may be less likely to exhibit amnestic profiles (memory impairment), and thus more likely to exhibit dysexecutive syndromes and visual spatial impairment. Cognitive decline in the presence of AD may occur at a slower rate in African Americans than NHWs[49, 29]. This distinct cognitive profile may contribute to the under-diagnosis of AD in African Americans, as AD diagnosis is biased towards memory complaints and rapid decline[12]. However, standard clinical assessments typically underestimate daily function and overestimate cognitive impairment in African Americans[50]. While the cognitive profile of African Americans with AD is well-characterized, we still do not know the cause of the cognitive disparities. The measurement tools themselves may not possess the nuanced cultural relevance required to address cognitive impairment in minority populations, as they were developed and validated in a homogenous Non-Hispanic White population [51,52,53]. Given the inaccuracies in cognitive assessment within African Americans, when comparing the relationship between cognition and other AD biomarkers, we must consider the underlying racial differences and normalize scores appropriately in statistical analyses[54–56].

1.5   Functional Neuroimaging

Neuronal dysfunction can be indirectly measured by changes in blood flow to regions of the brain using the Blood Oxygen Level Dependent (BOLD) signal[57]. This type of imaging, known as functional magnetic resonance imaging (fMRI), can detect functional changes in the framework and meaning of "functional networks". Structural changes occur well after cognitive changes can be detected in the trajectory of AD. Memory impairment usually begins before the hippocampus has noticeable atrophy, suggesting that neuronal dysfunctional precedes atrophy[58]. Figure 1 shows the progression of Alzheimer's disease, and when specific biomarker changes occur in the context of symptom emergence. This figure

indicates the utility of resting state (rs)-fMRI over structural MRI to detect differences between healthy

aging brains and those that show signs of dementia, and can be utilized throughout the disease spectrum.

Of note, this figure shows the emergence of tau markers after rs-fMRI changes begin. Because resting

state measures may not correlate with tau until an individual has reached a particular threshold of

amyloid, we will analyze tau and resting measures in individuals who have a clinically significant burden

of amyloid. The following sections will discuss the what is known about the functional profile of

Alzheimer's disease.
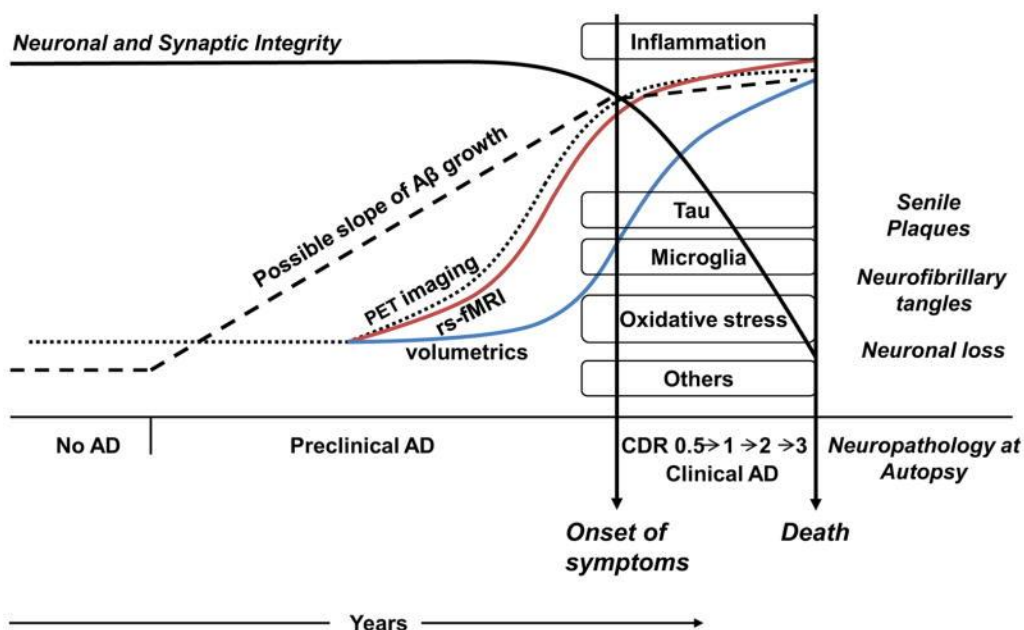
Figure 1 Timecourse from Preclinical to Clinical AD: Pathophysiology and Imaging. Taken from Sheline, et. al., 2013.

1.5.1 Default Mode Network in Alzheimer's Disease

Regions of the brain that exhibit highly correlated (or connected) BOLD single activity are

known as "functional networks". The default mode network (DMN) is perhaps the most commonly

studied functional network, particularly in dementia[59]. Typically, regions, or nodes, of the default mode

network include the ventromedial prefrontal cortex, the precuneus, posterior cingulate, and the inferior

parietal lobule[60,61], but others have divided the DMN into distinct functional subsystems[62], and others

include the hippocampus as part of this network[63]. In this work, we focus on connectivity measures between nodes of the DMN subnetworks.

Within Alzheimer's disease, lower connectivity between DMN nodes is the most commonly reported fMRI finding[58,64]. Within AD, connectivity typically decreases over time, and is lower among all regions of the DMN[65]. DMN connectivity also correlates with other AD biomarkers such as CSF Aβ42 levels, and hippocampal volumes such that as disease burden indicated by these biomarkers increases, DMN connectivity decreases[45,66]. However, DMN results are not consistent across all studies. Some studies have identified a spike in connectivity in the early stages of the disease, during a stage known as mild cognitive impairment (MCI), and then a gradual decline[67,68]. Some studies only report a decrease in connectivity between anterior and posterior DMN regions, and others indicate widespread DMN changes[59,63,65,69]. The reasons for these discrepancies may be methodological, but it is also possible that essential demographic variables, such as race, were not considered in the analysis. Because African Americans exhibit a unique phenotype of AD, and functional connectivity of the DMN is a potential a biomarker AD, it is important that racial differences in functional connectivity be explored. One aim of this work is to explore the correlates of DMN connectivity in individuals with Alzheimer's disease, and examine how race may modify connectivity relationships to other biomarkers.

1.5.2 *Racial Disparities in Functional Connectivity*

Functional connectivity has not been adequately explored in the context of racial differences. Most studies that investigate functional connectivity in African Americans either do not report the racial makeup of their sample[10], or recruit diverse samples, but do not include race as a factor of interest in statistical models[70,71], or only recruit African Americans[72,73,74]. We are by no means suggesting that these approaches are flawed, but to point out the literature examining racial disparities in functional connectivity profiles is essentially non-existent. Indeed, outright study of racial disparities must be thoughtfully conducted as it would be easy to utilize these findings to support discriminatory ideologies. However, if we are to understand the nature of racial disparities in Alzheimer's disease, explicitly

exploring racial differences is crucial. Because of the gap in the literature on this topic, we have looked to studies of racial disparities using other AD biomarkers to inform our hypotheses for this work, and we hope that these studies begin to fill this hole.

1.6 The Putamen in Alzheimer's Disease

While much of the research in dementia has centered around the DMN, there is evidence that regions outside the DMN may be effected by AD pathology, as far as 10 years out from symptom onset[75]. The putamen is region that is susceptible to both vascular disease[76,77] and the effects of AD[75]. This phenomenon has been observed in studies of pathology[78], positron emission tomography (PET)[79], and structural MRI[75], with little evidence from functional MRI in AD. Unlike the DMN, the putamen and its network nodes are responsible for cognitive performance outside memory domains, including executive functions, motor coordination, language processing, and visual spatial function[80,81]. Many individuals, including a larger percentage within the AA population[50], experience cognitive impairment in these domains in addition to memory[41]. Because the putamen is involved in these non-memory functions, but does exhibit vulnerability to AD, examining this region and its functional networks could provide a novel therapeutic target for interventions. However, we must first establish whether connectivity metrics within putamen networks correlate with known AD biomarkers.

Functional putamen networks are fairly well defined in the motor-disease literature[82,83]. Tractography and functional connectivity studies have identified the caudate, parts of the thalamus, superior frontal gyrus, middle frontal gyrus, and pre-and post-central gyri as regions most structurally and functionally connected to the putamen[84,83]. The anterior putamen has clear functional divisions on the anterior-posterior axis; the anterior putamen (APu) is classically viewed as a an associative region while the posterior putamen supports motor function [85]. The APu appears to be more affected by AD than its posterior counterpart in structural MRI[86,87,88] and atrophy of the APu better correlates with cognitive decline[75,89]. In this work, we investigate putaminal, specifically APu connectivity to further our understanding of the role of the putamen in AD. Additionally, because the putamen is vulnerable to both

AD and vascular disease, we will investigate the role of white matter hyperintensities (WMH) in putamen connectivity.

1.7   White Matter Hyperintensities

White Matter Hyperintensities are a significant risk factor for subsequent development of dementia, and are related to a number of lifestyle and biological factors[90]. White Matter Hyperintensities (WMHs) are damaged areas of periventricular and subcortical white matter that appear hyperintense on T2 weighted and Fluid Attenuated Inversion Recovery (FLAIR) scans[91]. Common neuropathological explanations of WMH include demyelination and axonal loss, endothelial dysfunction, and glial atrophy[91]. Their prevalence is variable in aging populations, and represent a risk factor for a host of neurological and cognitive complaints later in life such as an elevated risk of stroke or developing mild cognitive impairment[92]. Despite the prevalence of WMH in dementia, they are not specific to Alzheimer's Disease[92,93]. Although WMH are a risk factor for AD, their absence does not rule out AD, and they can occur without amyloid and tau pathology[94]. Lifestyle and biological factors can affect the presence of WMHs such that individuals who smoke[95], have diabetes[96], or cardiovascular disease[39] are at an increased risk of developing WMHs.

White matter hyperintensities (WMH) are a common finding in individuals with Alzheimer's disease (AD), but their etiologic role in AD is not well understood. There is an increasing debate as to where amyloid and tau can cause WMH, or whether amyloid and WMH have a synergistic relationship[98],[99]. Individuals with WMH typically have cognitive profiles different than those with "pure AD", the former causing generalized, but less severe, cognitive deficits, and the latter causing memory impairment [100]. However, recent evidence indicates that WMH could emerge independently of vascular disease and arise as a direct result of dementia, as an inflammatory response to amyloid beta plaques[101,102]. It is likely that the two pathologies have a synergistic relationship such that presence of WMH can increase vulnerability to AD pathology, particularly $A\beta_{42}$ plaques. In this work, we will

examine WMH and their correlation with CSF levels of tau and amyloid to determine whether the two AD biomarkers are related, and whether race modifies this relationship.

Some studies suggest that location of WMH determines whether they are AD related, or a result of vascular disease. WMH seem to have greater posterior involvement in individuals with AD, particularly in the parietal lobe[98,103]. Multiple studies have identified that the presence and volume of WMHs is greater in individuals with MCI and AD[92,98,104]. Some purport that WMHs provide a secondary neuronal insult that, in the presence of amyloid deposition, is necessary for the generation of AD[105]. Others cite the importance of the location of WMHs as indicative of disease processes, with AD particularly associated with posterior periventricular WMHs caused by tau[41,42,102]. In this work, we will examine the regional volume of WMH to determine if WMH in particular brain regions correlate with levels of CSF tau and amyloid which would support some type of causal mechanism between AD and WMH, and whether race modifies these relationships.

WMH can influence functional connectivity measures. WMH along tracts that are between grey matter regions of interest (ROIs) can influence connectivity, with connectivity decreasing as internodal WMH burden increases[106,107]. This is likely a result of the decline in neurovascular coupling that occurs in the presence of general vascular disease, and, more specifically, ischemic damage, of which WMH are a symptom[108]. We have chosen to focus on regions that are typically associated with AD (DMN), and regions vulnerable to both AD and vascular disease (putamen networks) to determine if the connectivity measures among these regions more strongly correlates with AD biomarkers or WMH to determine the nature of the functional connectivity alterations that we may identify.

1.7.1   *Racial Disparities in White Matter Hyperintensities*

WMH volume better predicts cognitive outcomes than hippocampal volumes in African Americans with dementia and Alzheimer's disease[49,109–112]. One explanation of this disparity is that African Americans are more likely than NHWs to exhibit mixed pathology in the presence of AD, particularly evidence of cardiovascular disease[113], and that it is consideration of these contributing co-morbidities in

the presence of AD pathology that predicts cognitive outcomes in this population[114]. Any functional connectivity differences that we identify between races may be attributable to differences between regional distribution of WMHs, as we have identified racial differences in the correlates of WMHs[115,116]. To date, no studies investigating differences between regional WMH volumes and functional connectivity in the context of race have been published.

1.8   Dissertation Aims

African Americans have a disproportionately high concentration of lifestyle risk factors, and are more likely to show mixed AD pathology when compared to NHWs. As previously mentioned, African Americans have higher rates of type-2 diabetes, that may have its roots in both genetic and lifestyle factors[117]. They also have higher rates of vascular disease, including atherosclerosis and peripheral vascular disease[118,119]. Both type-2 diabetes and vascular disease are risk factors for Alzheimer's disease[120–122]. African Americans have a disproportionately high level of environmental and lifetime stressors, which contribute to over poorer brain health[12]. African Americans, on average, experience more perceived stress than age and education matched NHWs, and these stressful life events have a greater negative impact on cognition[123,124]. African Americans are more likely to have a lower socioeconomic status, which usually carries with it substandard housing, low education, and unemployment, all of which are individual risk factors Alzheimer's disease[125–129]. It is difficult to delineate lifestyle from genetic factors when individuals with similar genetic backgrounds have similar life experiences and surroundings[130]. However, in our analyses we will include as many of these relevant potential mediators as possible, to uncover biological mechanisms that may explain racial differences.

African Americans have specific genetic risk factors for AD. The APOE e4 allele is more common in African Americans, and only one copy of the e4 variant is necessary to confer a greater AD risk for African Americans, unlike other races such as NHWs, in which two copies of the e4 allele are necessary to increase the risk of AD[131],[132]. This risk is not purely genetic, as studies with African Yoruba tribes show that two copies of the allele are required to increase the risk of developing dementia[133]. The

ABCa7 gene is also associated with increased risk of developing Alzheimer's disease within African Americans, but because the presence of the risk allele is highly collinear with race, its effect can only be analyzed within race[134,17]. Most of the studies that focus on these risk alleles logistically correlate the presence or absence of AD with presence or absence of one or two risk alleles. While useful in determining the whether a gene poses a risk, little is known about the disease mechanism behind the risk alleles and the subsequent effect on brain pathology. In our regression models, we will include the presence of APOE e4 as a factor, to determine if it is related to structural and functional neuroimaging measures.

The current set of diagnostic criteria may not be applicable to the broad population of individuals with AD. Most of the current models of Alzheimer's disease, and associated diagnostic cutoffs, have been generated in a primarily upper-middle class Caucasian population[19,135–137]. In order to expand current models of AD to a wider population, we must recruit individuals from more diverse backgrounds. African Americans often do not fit within the established diagnostic criteria, nor do they exhibit the same biomarker profile as NHWs[12]. Lower tau levels, weaker correlation between cognition and the regions of the brain most vulnerable to tau, and a higher prevalence of mixed pathology within African Americans point to a unique race-specific mechanism and disease trajectory yet to be defined by the scientific and medical community. Functional connectivity provides a method of examining neuronal alterations across the disease spectrum that can model the dynamic interactions between regions that may more accurately reflect cognitive changes, and respond to ischemic damage prevalent in the AA population.

Chapter 2 includes the analysis for Aim 1a, an analysis of default mode network connectivity and an analysis of the role race in connectivity to biomarker relationships in the context of dementia. Chapter 3 includes analyses for Aim 1b, which includes analysis of functional connectivity of the DMN and its subnetworks, and how these measures relate to regional hyperintensities, and the role of race. Chapter 4 includes both Aims 2 a & b; an analysis of putamen network connectivity, the role of hyperintensities, and how race modifies some of these relationships.

1.9   Specific Aims

1.9.1   Aim 1a: Determine the extent to which race modifies the relationship between connectivity of the DMN subnetworks and AD biomarkers.

1.9.2   Aim 1b: Determine the extent to which regional WMH account for racial differences we observe in DMN connectivity to biomarker relationships.

1.9.3   Aim 2a. Determine whether cortico-putamen connectivity correlates with AD biomarkers, and whether race modifies these relationships.

1.9.4   Aim 2b. Determine whether regional WMH relates to connectivity and accounts for any observed differences in connectivity to biomarker relationships.

The following manuscript originally appeared in Translational neurodegeneration as:

Misiura, M.B., Howell, J.C., Wu, J. *et al.* Race modifies default mode connectivity in Alzheimer's disease. *Transl Neurodegener* **9,** 8 (2020). https://doi.org/10.1186/s40035-020-0186-4

We have reprinted it here for the purposes of satisfying the dissertation requirements.

2 AIM 1A: RACE MODIFIES DEFAULT MODE CONNECTIVITY IN ALZHEIMER'S DISEASE

Maria B Misiura, M.A. [1,2], J. Christina Howell, B.A.[2], Junjie Wu PhD[3], Deqiang Qiu, PhD,[3], Monica W. Parker, M.D.[2], Jessica A.Turner, PhD[1], William T Hu, M.D., PhD.[2]

[1]Department of Psychology, Georgia State University. Atlanta, GA

Departments of [2]Neurology and [3]Radiology, Emory University. Atlanta, GA

Abstract

Background: Older African Americans are more likely to develop Alzheimer's disease (AD) than older Caucasians, and this difference cannot be readily explained by cerebrovascular and socioeconomic factors alone. We previously showed that mild cognitive impairment and AD dementia were associated with attenuated increases in the cerebrospinal fluid (CSF) levels of total and phosphorylated t-Tau in African Americans compared to Caucasians, even though there was no difference in beta-amyloid 1-42 level between the two races.

Methods: We extend our work by analyzing early functional magnetic resonance imaging biomarkers of the default mode network MRI between older African Americans and Caucasians. We calculated connectivity between nodes of the regions belonging to the various default mode network subsystems and correlated these imaging biomarkers with non-imaging biomarkers implicated in AD (CSF amyloid, total tau, and cognitive performance).

Results: We found that race modifies the relationship between functional connectivity of default mode network subsystems and cognitive performance, tau, and amyloid levels.

Conclusion: These findings provide further support that race modifies the AD phenotypes downstream from cerebral amyloid deposition, and identifies key inter-subsystem connections for deep imaging and neuropathologic characterization.

2.1 Introduction

It is not well understood why older African Americans are twice as likely to develop Alzheimer's disease (AD) as older non-Hispanic Caucasian Americans (abbreviated as Caucasian hereafter).[140,141] While vascular disease[12,126,142] has been speculated to contribute to the disparities in AD risks, genome-wide association and clinical studies suggest race/ethnicity (hereafter referred to as race), outside of these factors, also modify the molecular pathways implicated in the development and manifestation of AD pathology. For example, the *APOE* ε4 allele confers lower AD risks for African Americans than Caucasians,[135,143] the *ABCA7* risk allele confers greater AD risks for African Americans than Caucasians[17], and AD is associated with less amnestic baseline and slower longitudinal decline in African Americans than Caucasians on neuropsychological analysis.[42] These cohort-level differences may reflect intrinsic biological differences between race, lower correlation between clinically-suspected and pathologically-confirmed AD (~75% accurate), recruitment bias in one or both races, or a combination of these factors[27,144]. Data-driven strategies are therefore necessary to provide mechanistic correlates of observed race-associated differences to more clearly understand AD disparity.

One such approach is to use etiologic biomarkers associated with hallmark AD pathology to enhance the likelihood that those clinically suspected to have AD indeed have the pathology. We recently showed that in a group of older adults with mild cognitive impairment (MCI) or AD dementia, African Americans had lower cerebrospinal fluid (CSF) levels of t-Tau-related biomarkers than Caucasians[15]. This is despite similar changes in CSF levels beta-amyloid 1-42 (Aβ42). We interpreted these findings as preliminary evidence for divergent biomarker trajectories and these differences have now been validated in one independent cohort in St. Louis and an independent younger cohort in Atlanta [145,146].

Because we have not identified a difference in atrophy patterns between African Americans and Caucasians with AD, we hypothesized that rsfMRI would be a more sensitive approach to identify the effect of race on AD-related neurological changes. We are particularly interested in resting state functional connectivity, as alterations in connectivity can be detected well before disease onset[147] and track disease progression.[148] To explore brain changes associated with AD which may differ between

races, we analyzed functional connectivity (hereafter referred to as connectivity) in the default mode network (DMN) using resting-state functional MRI (rsfMRI). The DMN is considered a potentially useful imaging biomarker for AD that is more widely available than amyloid PET[65,68,149–152].

In older adults, the DMN is broadly defined as correlated Blood Oxygen Level Dependent (BOLD) signal among the precuneus, posterior cingulate cortex (PCC), the inferior parietal lobule (IPL), the ventromedial prefrontal cortex (vmPFC). [68,153] The DMN overlaps with anatomical sites vulnerable to amyloid deposition and atrophy in early AD, [154] and reduced connectivity between DMN nodes (intra-network connectivity) mirrors the stage-wise t-Tau deposition on PET imaging[45,155] even before there is detectable atrophy.[12] The trajectory of AD functional connectivity changes is complex. The overwhelming majority of studies examining four DMN nodes reported reduced connectivity in AD (dementia),[61, 156, 67, 157, 158] with an exception reporting increased connectivity during early MCI.[61] However, few studies used etiologic biomarkers to distinguish between cognitive impairment due to AD, psychiatric illness, or cerebrovascular disease[159]. DMN hyperconnectivity has also been observed in asymptomatic *APOE* ε4 carriers when compared to non-carriers,[160, 161] sometimes decades before symptom onset.[162] DMN connectivity may therefore have different relationships with AD risks (including risk genes), pathologic markers, clinical phenotypes, and disease stage, making inclusion of etiologic and clinical biomarkers in AD-related DMN analysis critical to ensure the consistency of findings.

As research on the DMN progresses, further fractionation of this complex network has revealed synchronous bold activity in regions outside traditional definitions of the DMN. Core subsystems[64] (dorsomedial, medial temporal lobe, and midline core) have been proposed to each contain key regions which work in tandem to support cognitive processes in learning and memory, retrieval of autobiographical information, self-referential processes,[163] and social processing[164]. Dividing the DMN into its subcomponents has thus far provided more sensitive timelines for disease progression in AD and other neurological disorders[156]. Studies have shown that connectivity within the medial temporal lobe, rather than average DMN connectivity between the four core nodes, more consistently relates to cognitive

impairment in AD[30,148]; increases in connectivity within the anterior subsystems during early AD is more consistently identified in studies analyzing DMN subsystems[34,157]; and memory impairment can be associated with decreased intra-subsystem connectivity within the medial temporal lobe[165] but increased connectivity between dorsomedial and midline core subsystems[166, 167].

The vast majority of studies analyze connectivity changes within diagnostic categories of normal cognition (NC), MCI, and AD dementia. Given that differences in cognitive impairment between NC and MCI and between MCI and AD dementia can sometimes be small, a continuous measure of cognition is preferred[168,169] especially when it remains controversial whether current diagnostic algorithms are valid in African Americans (even with race-adjusted norms)[12,49]. Thus, we also use a composite measure of cognitive performance derived from neuropsychological tests[15] to serve as a continuous, rather than categorical, measure of disease burden. We hypothesized that race modifies the relationship between connectivity and AD-related cognitive impairment, and between connectivity and two CSF AD biomarkers ($A\beta42$[170] and t-Tau[171]). Furthermore, we specifically tested the generalizability of AD-associated connectivity changes between DMN nodes and between DMN subsystems to extend the AD biomarker phenotype in African Americans.

2.2 Methods

Participants

This study analyzed previously collected data from a study that recruited self-reported Non-Hispanic Whites and African Americans over the age of 65 across the diagnostic spectrum of Alzheimer's disease dementia including individuals with normal cognition (NC), individuals with mild cognitive impairment (MCI), and individuals with Alzheimer's Disease (AD)[15]. The study was approved by the Emory University Institutional Review Board. Each participant underwent a detailed interview for demographic information, self-reported race (Caucasians of Hispanic or Latino ethnicity were not included in this study), vascular risk factors (coronary artery disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes, suspected transient ischemic attack), other medical

comorbidities (e.g., cancer), and medications (e.g., use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Each participant was then assigned a diagnosis according to consensus criteria including those for normal cognition (NC), MCI, and AD dementia (global Clinical Dementia Rating of 1 or 2.) Cognitively impaired subjects suspected of having a non-AD dementia (vascular, Lewy body, and frontotemporal dementia) were excluded. While our cohort was not age and gender matched specifically, we did not find significant differences in age between races or gender (Table 1). As previously reported, diabetes and hypertension were more common in African Americans than Caucasians, but had lower brain total white matter hyperintensity (WMH) volumes than Caucasians. Demographic data in table 1 refer to individuals who passed MRI quality control standards (n=137) as described below.

Cognitive, genetic, and CSF biomarkers

Neuropsychological analysis was performed as previously described[15]. Briefly, each subject underwent. Each subject also underwent a detailed neurologic examination and neuropsychological analysis for assessment of function in cognitive domains. These included(1) memory (Consortium to Establish A Registry for Alzheimer's Disease word list delayed recall, Brief Visual Memory Test–Revised [BVMT-R] delayed recall), (2) executive func-tion (Trail Making Test B, reverse digit span [RD], Symbol Digit Substitution Test, and letter-guided fluency), (3) language (Boston Naming Test [60 items], category fluency), and (4) visuospatial function (Judgment of Line Orientation[JOLO], Rey-Osterrieth complex figure test). With the exception of BVMT-R, JOLO, and RD, subtest Z-scores were calculated according to published normative data, adjusting for age, sex, education, and race. Z-scores for these three subtests were calculated using the same norms were used in Caucasians, but calculated using Atlanta-based, cognitively normal African Americans because published norms generated mean Z-scores of >2. Domain-specific Z-scores were calculated by averaging subtest Z-scores, and Z-scores for the four domains were averaged to generate composite cognitive Z-scores. Subjects with MCI and AD dementia had lower MMSE and cognitive Z-scores than subjects with NC (p <.01 for all comparisons, Table 1). In addition, each subject underwent standardized collection of blood (for *APOE* and *ABCA7* genotyping) and

CSF without overnight fasting according to a modified Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol as previously described.[34]

MRI acquisition and preprocessing

Each subject underwent MRI scanning using a modified ADNI protocol on a 3T scanner (Siemens AG) which included a T1-weighted 3D MPRAGE sequence (TR/TI/TE = 1620/950/3msec, flip angle = 30°, matrix = 192×256×160, and voxel size = 0.98×0.98×1mm³) and a 6 minute eyes-open resting state functional MRI scan (TR/TE = 3000ms/32ms flip angle = 90°, field of view (FOV) = 200 × 200 mm², acquisition matrix = 64 × 64, voxel size = 3.1 × 3.1 × 3.5 mm³, slice = 33, time point = 124) at the Emory Center for Systems Imaging. For rsf-MRI, we used the DPABI v4.0.190305 toolbox to preprocess the image data[172] after discarding the first 10 volumes to allow the magnetization to approach a dynamic equilibrium, and to allow for more time for our participants to get comfortable inside the scanner[158,173]. Individual echo-planar imaging (EPI) data were slice time corrected. Participants whose head motion exceeded 3.0 mm in translation or 3° in rotation were excluded. We further reduced the confound of head motion by higher-order regression based on Friston's 24-parameter model [174], and the effect of physiological artifacts by covarying signals from CSF space and white matter.[175] EPI data were normalized to a study specific template generated using the DARTEL algorithm in DPABI that is better suited for populations with larger amounts of atrophy than standard normalization to the MNI template.[176] A spatial filter of 6 mm full width at half maximum Gaussian kernel was used. Subsequently, a band pass temporal filter (0.01–0.08 Hz) was applied to reduce the low-frequency drifts and high-frequency noise.

MRI Quality Control

To be eligible for this analysis, participants must have had a T1 suitable for use in segmentation, as well as a usable resting state scan. To further eliminate confounds from head motion, we removed anyone whose mean framewise displacement (MWFD) was 3mm and higher[177]. Among 145 subjects, 8 (5%) had rsf-MRI that did not pass quality control and were excluded from DMN analysis. Table 1 displays demographic data only for individuals included in the MRI analysis (n=137), and Table 2 shows demographic data for individuals not included in the analysis. Compared to those included the

analysis, those excluded did not differ significantly in age, gender, diagnosis, or race. There was no significant difference in motion according to race or diagnosis.
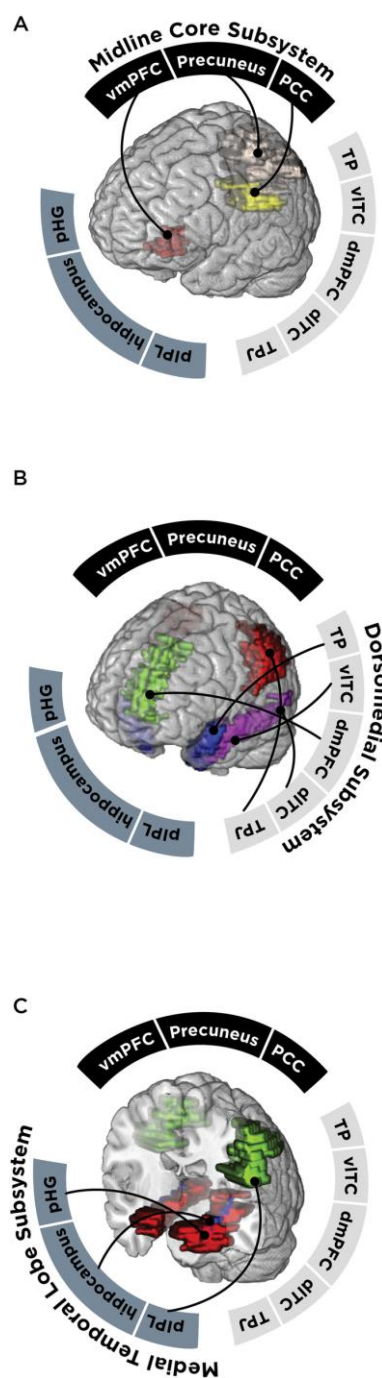
Figure 2 Empirically derived component maps of nodes according to each DMN subsystem. TP= temporal pole, vlTC= ventro-lateral temporal cortex, dmPFC= dorsomedial prefrontal cortex, dlTC= dorso-lateral temporal cortex, TPJ= temporal parietal junction,

Rsf-MRI Independent Component Analysis

We used a data driven approach (Independent Component Analysis; ICA) using the Group ICA of fMRI Toolbox v4.0b (GIFT) to identify large-scale brain networks.[178,179] We first performed independent components analysis with model-order of 80 to empirically derive our regions of interest which enabled us to break the DMN into its various subregions, while still maintaining appropriate degrees of freedom. ICA is a data driven approach that allows for more adaptation to individual subject variability, which is essential in special populations, particularly those with atrophy as in our sample. The Default Mode and its subnetworks are relatively robust, and can easily be identified in a higher order ICA model[148,180]. We chose an ICA approach as it can be more sensitive to sample characteristics, such as brain atrophy in older populations, than standard atlas based seed-regions while still accurately identifying regions of interest[181,182].

To identify our regions of interest, we correlated all non-artifactual components[183] with templates of the default mode network and chose components with the highest correlation values to the templates (0.80 cutoff threshold). Using the default mode network subdivisions and coordinates outlined by Andrews-Hanna,[64] we identified 11 components that contained our regions of interest for the DMN subsystems. Components were manually confirmed using the xjview toolbox(http://www.alivelearn.net/xjview/) to ensure that

they contained only our regions of interest. Regions included the temporal pole (TP), lateral temporal cortex (2 regions; ventrolateral (vlTC) and dorsolateral (dlTC), dorsomedial prefrontal cortex(dmPFC), and the temporal parietal junction(TPJ) which comprised the dorsomedial subsystem. The parahippocampal gyrus (pHG), hippocampus, and posterior inferior parietal lobule (pIPL) comprised the medial temporal lobe subsystem. Finally, the precuneus, posterior cingulate (PCC), and ventromedial prefrontal cortex (vmPFC) comprised the midline core subsystem (Fig. 1). We then calculated functional connectivity in GIFT by correlating the time courses of signal fluctuations between the chosen components, and obtained a correlation value for each region pair for a total of 55 measures of pairwise connectivity.

Statistical Analyses

Statistical analysis was performed in IBM SPSS 24.0 (Armonk, NY) and R version 3.3.3.[184] MANCOVA was used to determine if race modifies DMN connectivity according to cognition. First, we analyzed baseline connectivity differences (only within controls). Measures of intra-network connectivity between the DMN nodes were the dependent variables; cognitive scores, race, sex, age, and mean framewise displacement (MFWD) were independent variables. Next, we analyzed data from all participants using the same model, but included a higher order interaction term (race X cognitive scores). Separate models to additionally account for effects of *APOE* ε4, *ABCA7* risk allele, hypertension, total white matter hyperintensity (WMH) volume, cardiovascular risk score, and diabetes on DMN connectivity were also analyzed. For race-dependent connectivity changes, we accounted for multiple comparisons through the Benjamin-Hochberg method.[185] False discovery rate was limited to 10% given our sample size and the number of nominally significant interactions with race.

The same analysis was repeated according to Aβ42 levels in all subjects. Because there is significant overlap in t-Tau levels between NC and AD, we performed a third analysis according to t-Tau levels only in subjects with reduced Aβ42 levels (<192 pg/mL)[186]consistent with cerebral amyloid deposition.[187] Compared to using uncorrected nominal p<0.05 as a threshold, we reduced the number of

race-dependent node pairs from 23 to ten (six to four for cognition, from ten to two for CSF Aβ42, and from seven to four for CSF t-Tau). Because we observed an over-representation of race's effect on inter-subsystem connectivity between nodes belonging to the midline core and dorsomedial (midline-dorsomedial) subsystems regardless of the measure used for AD (cognition, Aβ42, t-Tau), we used bootstrapping (see below) to test whether the midline-dorsomedial connectivity was preferentially modified by race in AD compared to intra-subsystem and other inter-subsystem node pairs. Finally, as confirmation, we used analysis of covariance (ANCOVA) to determine whether race influenced the mean midline-dorsomedial connectivity, midline-temporal connectivity, and dorsomedial-temporal connectivity adjusting for diagnosis, age, and gender. Mean subsystem connectivity[156] was calculated by averaging, for each individual, all pairwise inter-subsystem node pair connectivity between the two subsystems in question (15 pairs in midline-dorsomedial, 9 pairs in midline-temporal, and 15 pairs in dorsomedial-temporal).

Bootstrapping

We developed a novel simulation-based approach to test whether there was empirical enrichment, or over-representation, for race modifying connectivity between midline core and dorsomedial subsystems. To determine the likelihood of a concentration of significant interaction terms occurring by chance alone, we first obtained p-values for all Race x Cognitive Z-score interaction term for all potential node pairings (n=55; all subjects), and repeated the process for Aβ42 (n=55; all subjects) and t-Tau (n=55; only in subjects with Aβ42 < 192 pg/mL).

As these AD features are inter-related, we pooled all 165 (55 x 3) p-values together, and used bootstrapping analysis ("boot" package in R,[188] with replacement) to create 1,500 simulated 3x5 (size of midline-dorsomedial matrix) matrices of p-values. The number of "chance-only" matrices (out of 1,500) with three or more significant p-values is thus the probability of an observed concentration in any random 3x5 matrix of node pairs resulting from chance alone. At the same time, because this probability can be artificially reduced by a more stringent threshold at the matrix level (e.g., four or more significant p-values), we created a second set of 1,500 simulated p-value matrices through the same bootstrapping

process to represent the range of possible midline-dorsomedial p-values. Instead of drawing from all

potential p-values, these 1,500 matrices were then only sampled from p-values pooled from the 45

interaction p-values between midline-dorsomedial node pairs (n=15 each for Race x Cognitive Z-score,

Race x Aβ42, and Race x t-Tau) (Figure 2). The probability of having three or more significant p-value

in each matrix in this second bootstrap is then compared with the first using Chi-squared test. We

compared the proportion of significant vs. non-significant p values across the two bootstrapped

distributions. The null hypothesis for this test was that the number of samples that contained more than

three significant p values would not differ between the midline-dorsomedial bootstrap and the chance-

only bootstrap. We elected to use 1,500 as the bootstrap size as it is well within the commonly

recommended threshold,[189] but still a tiny fraction of all possible combinations.
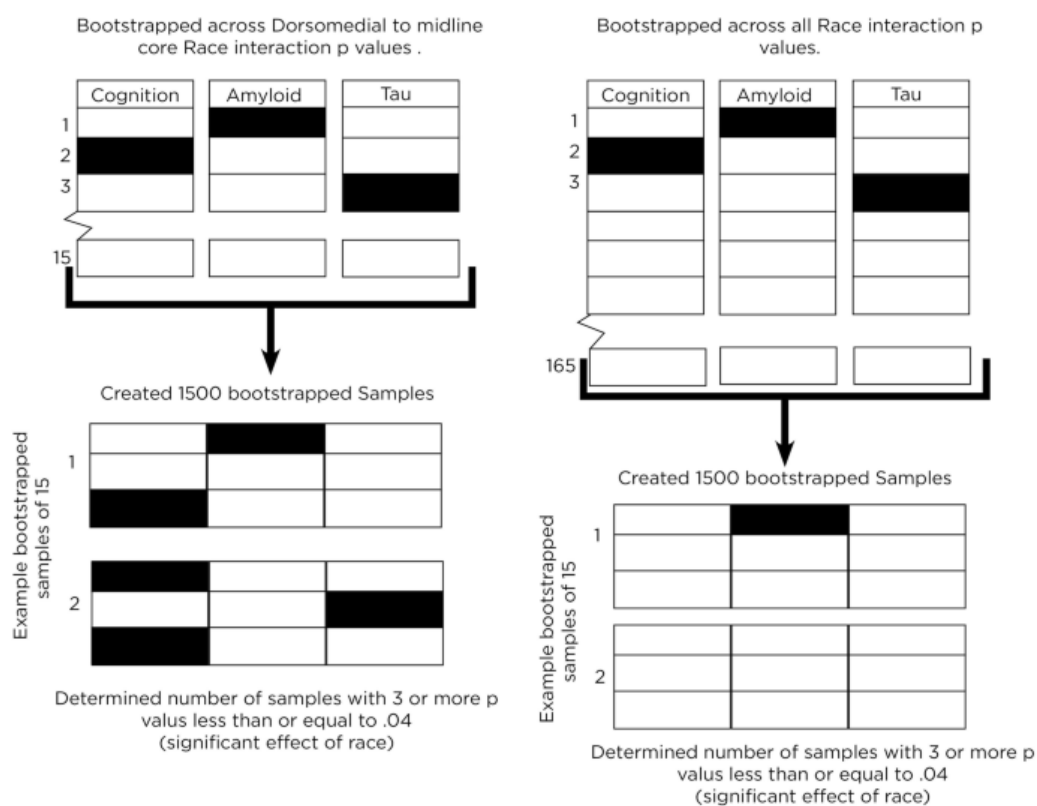
Figure 3 Illustrated workflow of the p-value bootstrapping analysis to confirm concentration of race's effect on midline-dorsomedial connectivity. Filled boxes represent node-pair connectivity modified by race, and empty boxes represent node-pair conne
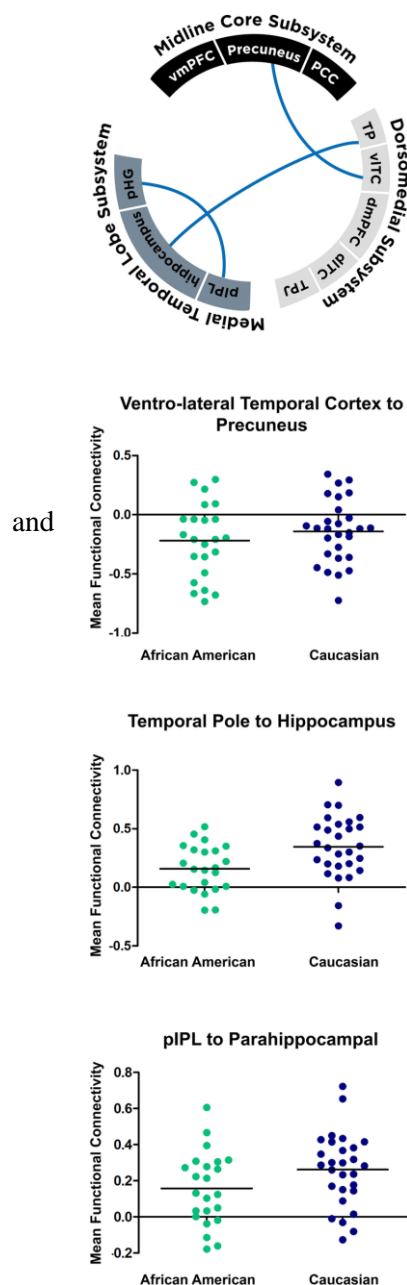
Figure 4 Baseline connectivity differences between older African Americans and Caucasians with NC (*p*<0.04). Among nodes distributed along the three subsystems, three node pairs' connectivity differed between the races. In all instances, African Americans (green) with NC had lower connectivity between these node pairs than Caucasians (blue; bars represent mean values). TP= temporal pole, vlTC= ventro-lateral temporal cortex, dmPFC= dorsomedial prefrontal cortex, dlTC= dorso-lateral temporal cortex, TPJ= temporal parietal junction, pIPL= posterior inferior parietal lobule, pHG=parrahippocampal gyrus, vmPFC= ventro-medial prefrontal cortex, PCC= posterior cingulate cortex.

2.3 Results

Baseline connectivity differences

We first compared baseline connectivity profiles between older African Americans and Caucasians with NC (n=58, Fig 3). Compared to Caucasians, African Americans had lower connectivity between the precuneus and the ventro-lateral temporal cortex (by 0.31, 95 %   CI -0.16, -0.46, p=0.01), the inferior parietal lobule parrahippocampal gyrus (by -0.15, 95 % -0.28, -0.03, p=0.01), and the temporal pole and hippocampus (by 0.19, 95 % CI -0.33, -0.04, p=0.01; Table 3). There were otherwise no baseline connectivity differences in the remaining 52 inter-nodal connectivity values between the two racial groups.

Race-independent changes centered in the medial temporal lobe subsystem of DMN

Because AD is characterized by reduced CSF Aβ42, increased CSF t-Tau, and cognitive impairment, we first analyzed the relationship between DMN connectivity, AD biomarkers (cognitive Z-score, Aβ42, t-Tau), and race to determine when race did not modify the relationship between AD biomarker and connectivity. In both African Americans and Caucasians, lower (more abnormal) Aβ42 levels correlated with decreased connectivity between the inferior parietal lobule and the parrahippocampal gyrus (*B*= -.01, *t*(167)=-2.14, *p* =0.02). Because there is overlap in CSF t-Tau and p-Tau$_{181}$ levels between

controls and AD even though their levels are elevated at the group level, we restricted t-Tau-related

analysis to those with Aβ42 levels consistent with AD (< 192 pg/mL).

This also showed higher (more abnormal) t-Tau levels to correlate with decreased connectivity

between multiple region pairs within the DMN, including hippocampus-temporal pole (*B*= .04,

t(167)=1.58, *p* =.02) (Figure 4). Connectivity correlated with cognitive impairment regardless of race

appeared to occur between the medial temporal lobe and the midline core subsystems, and between the

medial temporal lobe and the dorsomedial subsystems (Table 4, Figure 4).
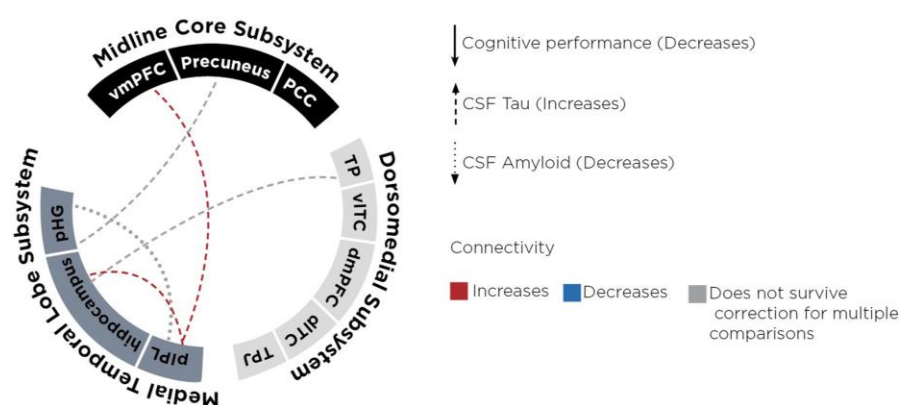
Figure 5 Race independent connectivity associations with biomarkers. Lines represent regions
pairs for which connectivity was significantly related to the particular AD biomarker regardless of race
(dashed line indicate CSF tau, solid line indicates cognition, and dotted line indicates CSF amyloid, red
for positive relationship, blue for negative relationship, and grey for a relationship that did not survive
correction for multiple comparisons). TP= temporal pole, vlTC= ventro-lateral temporal cortex, dmPFC=
dorsomedial prefrontal cortex, dlTC= dorso-lateral temporal cortex, TPJ= temporal parietal junction,
pIPL= posterior inferior parietal lobule, pHG=parahippocampal gyrus, vmPFC= ventro-medial prefrontal
cortex, PCC= posterior cingulate cortex.

Race selectively modified the relationship between AD biomarkers and connectivity only

between the MTL and Dorsomedial subsystem nodes

We next examined node pairs whose connectivity relationship with AD biomarkers was modified

by race (Table 5, Figure 5). In Caucasians, greater cognitive impairment was associated with decreased

DMN connectivity between the precuneus and lateral temporal cortex, and between the precuneus and the

temporal pole. However, the opposite is true in African Americans, with greater cognitive impairment

associated with *increased* connectivity between these same regions. Similarly, lower (more abnormal)

Aβ42 levels correlated with greater connectivity between the precuneus and both lateral temporal cortex and dorsomedial prefrontal cortex only in African Americans. Higher t-Tau levels (in those with Aβ42 levels < 192 pg/mL) also correlated with greater connectivity between the lateral temporal cortex and precuneus, and between the temporal pole and both vmPFC and precuneus, and between the hippocampus and PCC, again only in African Americans. Adjusting for risk genes (*ABCA7*, *APOE)* and other factors (hypertension, cardiovascular risk score, white matter hyperintensities, and diabetes) did not significantly influence connectivity values and race-associated differences persisted in connectivity relationship.
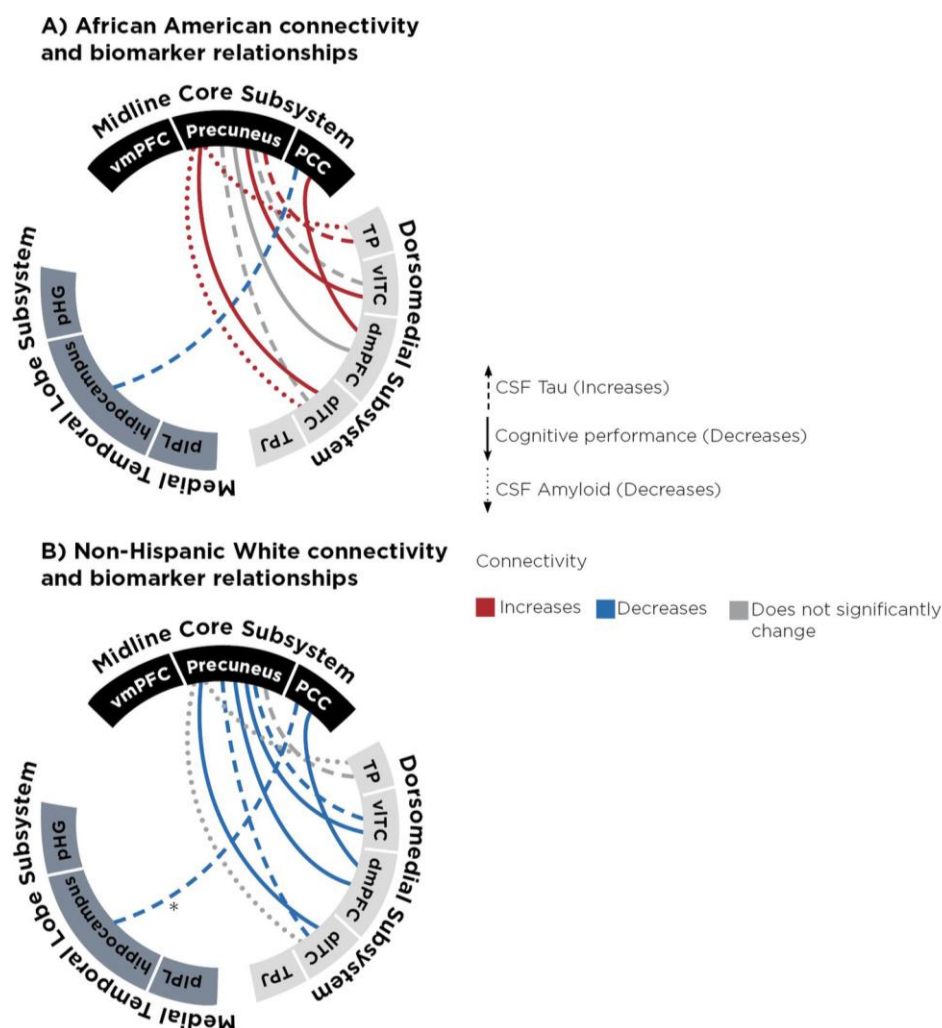
Figure 6 Connectivity and biomarker relationships in African Americans for which interaction term regression coefficient (race X biomarker) is significantly greater than zero. Figure depicts regression relationship between connectivity and biomarkers in African Americans. Red line indicates connectivity increases as disease burden for that biomarker increases (see indication for each biomarker). Blue line indicates connectivity significantly decreases as disease burden for that biomarker increases (see indication for each biomarker). Gray outline indicates no significant relationship for African Americans

between connectivity and biomarker. Dashed line indicate CSF tau, solid line indicates cognitive performance, and dotted line indicates CSF amyloid. *=NHWs had significantly stronger (more negative) relationship than AAs. TP= temporal pole, vlTC= ventro-lateral temporal cortex, dmPFC= dorsomedial prefrontal cortex, dlTC= dorso-lateral temporal cortex, TPJ= temporal parietal junction, pIPL= posterior inferior parietal lobule, pHG=parahippocampal gyrus, vmPFC= ventro-medial prefrontal cortex, PCC= posterior cingulate cortex.

Visualizing race-independent (Fig 4) and race-dependent (Fig 5) DMN changes in AD, we observed a pattern of race-specific changes involving connectivity between two subsystems. Whereas race-independent connectivity occurred between each pair of subsystems, nine out of ten race-dependent connectivity changes were between the midline core and dorsomedial subsystems. For each subject, we calculated a mean connectivity value by averaging the all node-pair connectivity values between two subsystems.

We further tested whether the midline-dorsomedial connectivity had an over-representation of node pairs whose connectivity was modified by race compared to the rest of DMN, we used bootstrapping (with replacement) to create 1,500 simulated 3x5 matrices drawn from midline-dorsomedial node pairs and 1,500 simulated matrices drawn from all node pairs. We found that drawing from the midline-dorsomedial matrices was more likely to result in identifying at least three significant race X AD biomarker effect than drawing from all node pairs: 791/1500 in the midline-dorsomedial sample vs. 192/1500 in the chance-only sample, X^2 (2, N=3000)=487.53, p= 0.00001. ANCOVA adjusting for diagnosis, age, and gender confirms a main effect for race (F(2, 119)=3.255, p=0.074) for mean midline-dorsomedial connectivity, but not for mean midline-temporal connectivity (F(2,119)=0.061, p=0.8060) or mean dorsomedial-temporal connectivity (F(2,119)=1.418, p=0.236).

2.4 Discussion

Consistent with previous work, we found AD to alter connectivity between the medial temporal lobe and dorsomedial subsystems, but we identify race-specific changes associated with these alterations [190,191]. Importantly, we extend the effect of race on AD-related connectivity from the inter-nodal level to the inter-subsystem level through a novel analytical strategy. To the best of our knowledge, this is the

first attempt to statistically identify enrichment of a factor's effect on connectivity between two subsystems across multiple related measures (cognition, Aβ42, t-Tau). The implication of this inter-subsystem effect is not well understood. Other conditions previously observed to confer similar specificity on inter-subsystem connectivity include PTSD,[192] depression,[193] and schizophrenia.[194] Interestingly, some of these conditions show racial disparities (schizophrenia[195] and PTSD[196] are more common in African Americans than Caucasians). The inter-subsystem specificity may reflect shared vulnerability to neuropsychiatric disorders in African Americans, existence of disease subtypes, or divergent disease-associated pathways. We discuss these possibilities in the context of AD in African Americans below.

In contrast to a uniformly slow disease process in African Americans, it is also possible that the multiple pathologic processes in AD may not proceed at the same pace in African Americans. In post-mortem studies of AD (involving primarily Caucasians), Aβ42-rich neuritic plaques are found early in the medial temporal as well as neocortical regions[154]. In contrast, tau-related changes appear in the medial temporal lobe before a stage-wise involvement of the frontal and then parietal cortical regions[154]. If we can interpret these observations as early co-localization of neuritic plaques and neurofibrillary tangles in the medial temporal lobe, the race-independent effect on inter-subsystem connectivity involving this region is in keeping with shared early AD changes by older African Americans and Caucasians when CSF Aβ42 alterations are detectable. The attenuation of midline-dorsomedial connectivity in African Americans could then be interpreted as early compensation when AD is mild, or as pathological hyper-connectivity [197,198]. This would support the diminished cognitive reserve hypothesis in African Americans (potentially due to vascular disease[199]), and the prevailing longitudinal models that African Americans have slower decline in the presence of AD pathology.[12,200] At the same time, the correspondence between ante-mortem DMN connectivity changes and post-mortem lesional mapping is known to be imperfect. For example, we found connectivity involving the posterior inferior parietal lobule (pIPL, a node in the medial temporal lobe subsystem) to be affected by AD independent of race. This may suggest pIPL to be a locus of early AD pathology, but neurofibrillary tangles do not appear in this region until later in AD.[201]

The identified disparities in cognition and its relationship to functional connectivity are in keeping with current understanding of the African American cognitive profile in AD. African Americans exhibited an inverse relationship between cognition and FC compared to Caucasians such that as cognitive impairment increased, connectivity also increased. Typically, in AD, connectivity decreases as cognitive impairment increases. However, an increase in connectivity can be a result of disease processes[198]. An increase in connectivity in the mild cognitive impairment stage of AD, and in the presence of vascular disease is a fairly common finding[199]. Africans Americans generally exhibit slower cognitive decline in AD, and this increased connectivity could reflect an extension of early disease processes that generate the increased connectivity seen in many MCI studies.

Other than milder AD-related tau pathology, the selectivity of race for midline-dorsomedial connectivity could result from non-AD pathologies outside these two subsystems or neuro-protective changes along the tracts connecting two subsystems. Limited autopsy studies have shown African Americans more likely than Caucasians to have mixed AD and vascular lesions,[114] and we previously showed in this cohort that African Americans experienced greater cognitive impact than Caucasians from the same degree of WMH.[15] In the current study, we did not find total WMH volume to be related to race and connectivity. However, the impact of regionally specific WMH has yet to be examined. The baseline differences in connectivity suggest existing differences in brain function separate from disease mechanisms that could be related to vascular disease, but the nature of these differences is not well understood, and the inclusion of vascular disease in our regression models did not alter our results. Although hypertension was more prevalent in our African American cohort, and African Americans had elevated cardiovascular risk scores, when we included this variable in our analyses, it did not explain the variability associated with race. Our identification of race-associated changes in midline-dorsomedial connectivity would support a search for WMH changes outside of these two subsystems. Alternatively, Caucasians may be more likely to have WMH between these two subsystems.[202] The vascular load in our cohort was mild to moderate, as it is not feasible, or ecologically valid to recruit older patients with minimal vascular disease. There are a variety of risk factors and contributing comorbidities for

Alzheimer's Disease. It is possible that the various risk factors associated with AD may be different across different ethnic groups, such that AAs may have an increased vascular component of AD, while exhibiting AD pathology sufficient to meet diagnostic thresholds. WMH and AD are not mutually exclusive, and many have stated that WMH are a core feature of AD[203],[116], and a better predictor of disease burden in African Americans[204]. Future research will explore region-specific WMH between races and whether these differences relate to observed connectivity biomarker relationships.

It would be remissive to not explore social factors which may contribute to these biological disparities. The current work is the first to establish AD-related connectivity difference between races, and extends the neurobiological phenotype of AD in African Americans beyond a higher prevalence. How historical and current social inequalities may interact with genetic and environmental risks to give rise to these biological endpoints remains unknown. A variety of social disparities including income (amount vs. purchasing power), education (length vs. quality), and discrimination may additively or synergistically converge on the same biological endpoints. When analyzed separately, these factors may individually correlate with racial disparity but fail to capture the entire range of exposures facing different groups. For example, individuals who experience racial discrimination and perceive it as such are more likely to have higher blood pressure and increased psychological distress,[205,206,207] which in turn are risk factors for AD.[208] Chronic stress also increases connectivity between the DMN and other networks at least in young adults,[209] and may in part account for baseline and AD-related connectivity differences between the two racial groups. We did not include household income as a surrogate measure of lifelong socioeconomic status because the two measures poorly correlate in retired people, and the sample size limited our ability to interpret results when we introduced a measure such as the Area Deprivation Index[210]. A larger sample size will be necessary to test mediation effects between discrimination, stress, cardiovascular disease, and negative health outcomes, and cohort studies need to explore biologically meaningful methods to characterize individual and group-based experiences of injustice.

While we present the first biomarker-informed analysis of DMN inter-subsystem connectivity in African Americans, there are a number of limitations to our study. We tested two common AD risk

genotypes as mediators for race-associated differences, but we did not perform extensive genomic association analysis because of sample size. While we observed multiple race-associated differences in DMN connectivity using ICA, we did not perform seed-based analysis of other large-scale brain networks (e.g., salience network). This cohort's African American participants had similar years of education and socioeconomic status as their Caucasian counterparts, but other medical, psychiatric, or psychosocial differences could contribute to inter-subsystem connectivity differences. We did not identify a modifying effect of race on mean connectivity strength between the MTL and dorsomedial subsystem. Lastly, both racial groups include heterogeneous genetic backgrounds and in some cases mixed genetic heritage, so our results should be interpreted at the cohort level rather than the individual level. Nevertheless, we present additional evidence that AD is associated with systematic biomarker differences between older African Americans and Caucasians. Because CSF t-Tau-related findings similar to ours were replicated in a separate US cohort,[2] independent replication of these DMN findings will further highlight the importance of diversity, inclusion, and disparities in on-going effort to elucidate mechanism-related biomarkers in AD.

2.5 Conclusions

We previously identified that African Americans and Caucasians share the same AD-associated CSF alterations related to amyloid deposition, but different CSF t-Tau biomarker levels regardless of AD status.[15] Here we extend our findings to show older African Americans and Caucasians have similar AD-associated subsystem connectivity changes involving the medial temporal subsystems. However, we also demonstrate race-specific patterns of connectivity between the midline core and dorsomedial subsystems, that are in-line with current studies that suggest divergent tau relationships between races. Race modified the relationships between AD biomarkers and connectivity between the medial temporal lobe and dorsomedial subsystems. We thus propose adding DMN connectivity to the list of biomarkers with race-dependent alterations in AD. Similar to CSF, rsfMRI profiles for AD established in pre-dominantly Caucasian cohorts may under-diagnose the disease when applied directly to African Americans, and

negatively impact the interpretation of clinical trial outcomes when rsfMRI is used as surrogate marker of AD. The current work further provides specific regions of interest for imaging-based and molecular investigation of disease mechanisms.

2.6 Chapter 2 Tables

Table 1 Demographic information. Sample reported here is the final imaging cohort of all individuals who passed imaging quality control. Note: T-tests were performed to compare races in the whole cohort and within each diagnostic category. *p<.05, **p<.001. MMSE and CogZ scores were significantly different between diagnostic categories such, NC having highest MMSE scores and AD having lowest(MMSE: NC vs MCI, p= .007, MCI vs AD, p<.0001, CogZ: NC vs MCI, p<.0001, MCI vs AD, p<.0001).

	Overall (N=137)		Normal cognition		MCI		AD	
	Caucasian (n=72)	African American (n=65)	Caucasian (n=31)	African American (n=27)	Caucasian (n=25)	African American (n=28)	Caucasian (n=16)	African American (n=10)
Age, years (SD)	70.90(7.84)	69.20(7.49)	71.65(8.39)*	67.48(6.17)*	71.52(5.82)	70.07(7.74)	68.50(9.41)	71.4(9.65)
Gender	35(37)	43(29)	19(12)	17(10)	15(10)	12(16)	9(7)	6(4)
Years of Education (SD)	16.32(2.85)	16.15(2.85)	16.81(2.69)	15.78(2.66)	17.08(2.58)	16.29(2.81)	14.19(1.94)	16.80(3.55)
MMSE (SD)	26.32(4.90)	26.91(3.57)	28.84(0.86)	28.00(1.86)	27.64(1.68)	26.67(2.34)	21.37(3.38)	20.22(6.18)
Cognitive Z Scores (SD)	-0.78(1.12)	-0.72(0.99)	0.07(0.51)	0.11(0.51)	-0.88(0.86)	-0.67(0.59)	-2.24(0.66)	-2.36(1.02)
White Matter Hyperintensity volume (mm^3)	3984.40 (4110.10)	3886.03 (4964.93)	3306.81 (3337.32)	2440.93 (2576.15)	4018.66(4080.03)	4313.70(5330.60)	5243.68(5333.14)	6730.21(7607.48)
Having *ABCA7* risk allele, (%)	23.67*	43.10*	29.00	44.40	24.00	50.00	12.50	30.00
Have Diabetes, (%)	5.67**	33.80**	6.50**	33.33**	0*	28.60*	12.50*	50.00*
Have Hypertension(%)	45.83**	72.31**	45.16	62.96	56.00	78.57	31.25*	80.00*
CSF Aβ42, pg/ml (SD)	148.35(95.02)	168.48(128.86)	199.93 (132.30)	165.27 (89.8)	199.11 (141.02)	134.69 (90.99)	77.65(47.39)	133.55 (140.71)
CSF t-Tau, pg/ml (SD)	72.84(49.63)**	40.92(20.79)**	51.68 (30.96)**	36.04 (11.63)**	63.99 (33.71)*	35.44 (13.67)*	108.48 (77.43)	75.8 (33.52)
CSF p-Tau, pg/ml (SD)	17.58 (8.97)**	25.81 (12.47)**	23.47(9.71)**	14.05 (5.07)*	25.01 (13.42)*	17.74(7.21)*	33.53(14.64)	24.54(10.27)
CSF t-Tau/Aβ42	0.73 (0.91)*	0.24 (0.22)*	0.46(0.74)*	0.15 (0.12)*	0.44(0.42)*	0.22(0.14)*	1.36(1.16)	0.55(0.41)

Table 3

	Overall (N=8)		Normal cognition		MCI	
	Caucasian (n=5)	African American (n=3)	Caucasian (n=4)	African American (n=2)	Caucasian (n=1)	African American (n=1)
Age, years (SD)	69.78(5.83)	65.20(10.25)	71.65(8.39)	67.48(6.17)	71.52	70.07
Years of Education (SD)	16.82(2.85)	16.25 (2.63)	16.8(2.69)	16.78(2.66)	17.08	16.29
MMSE (SD)	27.82(4.90)	28.91(3.57)	28.9(0.86)	27.75(1.86)	27.64	26.67
Cognitive Z Scores	0.89(2.62)	0.82(1.89)	-0.02(0.62)	0.01(0.71)	0.84	0.75
Having *ABCA7* risk allele, (number)	1	2	0	1	1	1
Have Diabetes, (number)	0	1	0	1	0.0	0
Have Hypertension (number)	2	2	1	1	1	1
CSF Aβ42, pg/ml (SD)	133.34 (95.02)	139.81(140.36)	200.93(132.40)	164.27 (98.6)	201.11	134.69
CSF t-Tau, pg/ml (SD)	72.84(49.63)	40.92(20.79)	51.68(30.96)	36.04(11.63)	63.99	35.438
CSF p-Tau, pg/ml (SD)	42.71 (20.98)	29.90 (15.60)	37.44 (16.29)	22.95 (8.46)	29.65	17.25
CSF t-Tau/Aβ42	0.79(0.81)	0.26(0.21)	0.85(0.87)	0.15 (0.16)	0.46	0.22

Table 2 Demographic information for individuals excluded from analysis who did not pass QC

Connectivity	B (95% Confidence interval)	Unadjusted p	Storey's q
Temporal Pole to Hippocampus	-0.19(-0.33, -0.04)	0.01	0.137
Ventro-Lateral Temporal Cortex to Precuneus	**-0.31(-0.46, -0.16)**	**0.01**	**<0.001**
Inferior Parietal Lobule to Parrahippocampal gyrus	-0.15(-0.28, -0.03)	0.01	0.495

Table 3 Baseline differences in functional connectivity between African Americans with NC and Caucasians with NC, adjusting for age, gender, and APOE ε4 allele.

Subsystems	Connectivity	Factor	B (95% Confidence Interval)	Unadjusted p	Storey's q
MTL to MTL	Posterior IPL to Hippocampus	Race	0.019(-0.29, -0.05)	0.387	
		t-Tau	**0.002(0.00, 0.003)**	**<0.001**	**<0.001**
	Posterior IPL to Parra-Hippocampal gyrus	Race	0.32(-0.14, .25)	0.710	
		Aβ42	0.02(0.008, 0.40)	0.010	1.000
MTL to midline core	Posterior IPL to Ventromedial prefrontal cortex	Race	-0.05(-0.30, 0.20)	0.675	
		t-Tau	**0.002(0.00, 0.003)**	**0.001**	**0.004**
	Parra-Hippocampal gyrus to Precuneus	Race	-0.10(-0.30, 0.23)	0.358	
		t-Tau	0.002(0.00, 0.002)	0.008	0.147
MTL to dorsomedial	Temporal Pole to Hippocampus	Race	-0.10(-0.30, 0.10)	0.337	
		t-Tau	0.002(0.00, 0.003)	0.009	0.247

Table 4 Factors associated with AD biomarkers (unadjusted p ≤ 0.01) independent of race, adjusting for age, gender, mean framewise displacement, and *APOE* ε4 allele. Unadjusted p-values which remain significant after Benjamini-Hochberg step-up correction for multiple comparisons are bolded. Storey's q-values are also shown with FDR < 10%. MTL= Medial Temporal Lobe. IPL= inferior parietal lobule.

Subsystem	Connectivity Pair	Variable Name	B(95 % Confidence Interval)	Unadjusted p	Storey's q
Dorsomedial to midline core	Dorsomedial prefrontal cortex to precuneus	Race	-0.02(-0.30, 0.25)	0.861	
		Cognitive impairment	0.04(-0.13, 0.04)	0.292	
		Race * Cognitive impairment	**-0.14(0.07, 0.25)**	**0.005**	**0.092**
	Ventrolateral temporal cortex to precuneus	Race	-0.24(-0.59, 0.11)	0.170	
		Cognitive impairment	-0.08(-0.02, 0.19)	0.103	
		Race * Cognitive impairment	**0.18(0.02, 0.17)**	**0.001**	**0.055**
		Race	-0.05(-0.32, 0.21)	0.695	
		t-Tau	-0.003(-0.02, -0.002)	0.712	
		Race * t-Tau	**0.02(-0.03, -0.0002)**	**0.001**	**0.055**
	Dorsomedial prefrontal to posterior cingulate cortex	**Race**	**0.29(0.08, 0.50)**	**0.007**	
		Cognitive Impairment	0.05(-0.15, 0.03)	0.407	
		Race * Cognitive impairment	**0.18(0.02, 0.17)**	**0.007**	**0.096**
	Temporal Pole to precuneus	Race	0.05(-0.18, -0.29)	0.667	
		Aβ42	0.0003(0.00, 0.01)	0.345	
		Race * Aβ42	**-0.001(-0.002, -0.00001)**	**0.004**	**0.073**
		Race	-0.80(-0.29, 0.13)	0.442	
		t-Tau	-0.002(-0.01, -0.001)	0.736	
		Race *t-Tau	**0.003(0.001, 0.006)**	**0.005**	**0.069**
	Dorso-lateral temporal cortex to precuneus	Race	-0.21(-0.12, 0.36)	0.112	
		Aβ42	0.0002(-0.0001, 0.01)	0.345	
		Race * Aβ42	**-0.002(-0.003, -0.00001)**	**0.002**	**0.055**
		Race	-0.21(-0.43, 0.02)	0.070	
		t-Tau	-0.001(-0.002, -0.02)	0.066	
		Race * t-Tau	**0.004(0.001, 0.006)**	**0.003**	**0.083**
		Race	**-0.074(-0.20,0.54)**	**0.004**	
		Cognitive impairment	**0.27(-0.04,0.09)**	**0.001**	
		Race * Cognitive impairment	**0.20(0.05, 0.25)**	**0.002**	**0.055**
MTL to midline core		Race	-0.001(-0.22, 0.22)	0.900	
		t-Tau	-0.001(-0.03, 0.002)	0.199	

	Posterior cingulate to hippocampus	**Race * t-Tau**	**0.003(0.001, 0.052)**	**0.004**	**0.073**

Table 5. Factors differentially associated with AD biomarkers according to race (unadjusted p≤0.01), adjusting for adjusting for age, gender, mean framewise displacement, and *APOE* ε4 allele. Unadjusted p-values which remain significant after Benjamini-Hochberg step-up correction for multiple comparisons are bolded. Storey's q-values are also shown with FDR < 10%. MTL= Medial Temporal Lobe. IPL= inferior parietal lobule.

3   Aim 1B: WHITE MATTER HYPERINTESITIES DO NOT ACCOUNT FOR CONNECTIVITY DIFFRENCES ACCORDING TO RACE.

3.1 Introduction

Previous research has identified race associated differences between brain connectivity and Alzheimer's disease burden[209]. As defined by Andrews-Hanna, the default mode network is composed of 3 functionally distinct subsystems (dorsomedial, midline core, and medial temporal subsystem)[190]. Connectivity between the default mode network typically declines as Alzheimer's disease progresses[59]. However, this finding has primarily been replicated in Non-Hispanic Whites (NHWs) with middle to high socio-economic status[20]. In a previous study, we investigated Alzheimer's disease biomarkers in the form of CSF tau, Aβ42, and cognitive performance and their relationship to default mode subsystem connectivity in a sample including both African Americans and NHWs. Within NHWs, as AD disease burden increased, connectivity between the dorsomedial and midline core subsystems typically decreased. However, within African Americans, as disease burden increased, connectivity between these same subsystems increased, even after for controlling for APOE e4 phenotype, and total WMH volume. A potential explanation for this discrepancy was that African Americans had differences in the regional distribution of white matter hyperintensities, as AAs had higher percentages of vascular disease and type 2 diabetes[210]. As the regional white matter hyperintensity volumes became available, we analyzed the plausibility of this explanation. In this study, we examined regional white matter hyperintensities in DMN subsystems, as well as other subcortical structures to determine whether WMH explained the increase in connectivity relate to AD observed in African Americans.

3.2 Methods

Participants

We used previously calculated functional connectivity values of a cohort that was ethnically similar to our previously studied cohort, with the exception that this cohort did not contain any AAs with Alzheimer's disease (only NC and MCI). Briefly, each participant underwent a detailed interview for

demographic information, self-reported race (Caucasians of Hispanic or Latino ethnicity were not included in this study), vascular risk factors (coronary artery disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes, suspected transient ischemic attack), other medical comorbidities (e.g., cancer), and medications (e.g., use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Each participant was then assigned a diagnosis according to consensus criteria including those for NC, MCI, and AD dementia (global Clinical Dementia Rating of 1 or 2.) Cognitively impaired subjects suspected of having a non-AD dementia (vascular, Lewy body, and frontotemporal dementia) were excluded. Information for this cohort is available in the "cohort 1" information in chapter 4, table 1.

MRI data collection & Analysis

Scanning protocol included a T1-weighted 3D MPRAGE sequence (TR/TI/TE = 2400/1060/2.31msec, flip angle = 8°, matrix =320x300, and voxel size = 0.8×0.8×0.8mm^3) and a 6 minute eyes-open resting state functional MRI scan (TR/TE = 724ms/32ms flip angle = 52°, field of view (FOV) = 220 × 220 mm^2, acquisition matrix = 104 × 104, voxel size = 2 × 2 × 2 mm^3, slice = 91, time point = 550), and a T2-weighted Fluid attenuated inversion recovery (FLAIR) scan (TR/TI/TE = 9000/2500/91 msec, flip angle = 150°, matrix =256x256, and voxel size = 0.8×0.8x5mm^3).

We conducted preprocessing pipelines with identical procedures for each cohort. To control for the difference in scanning parameters, we included cohort as a fixed effect in our statistical models. We utilized a standard preprocessing pipeline utilizing the DPARSFA toolbox [170]. The first 10 timepoints were removed, scans were slice time corrected, manually re-oriented, realigned, normalized and smoothed using the DARTEL & algorithm[211]. This algorithm is more appropriate than standard normalization to the MNI template for special populations, such as those with atrophy. We then performed nuisance covariate regression (Friston's 24 parameter head motion regressors, CSF, WM). We further removed motion-confounds using ICA-AROMA and applied a high pass filter.

Regional WMH analysis

Regional WMH volumes were derived from T2-weighted fluid-attenuated inversion recovery images software developed by researchers in the Brickman Lab at Columbia University [212]. Briefly, each participant's fluid-attenuated inversion recovery image was corrected for intensity normalization, then skull-stripped and intensity normalized again. The skull-stripped images were sent through a high pass filter at the mode of the distribution of the image voxel intensity values. A half Gaussian mixture model was fit to the log-transformed histogram of the intensity values of each image. The Gaussian distribution that encapsulated the highest intensity values defined the hyperintense voxels and was labeled. Any cluster of labeled voxels that comprised fewer than five voxels was removed from the mask. The labeled images were visually inspected and false positives removed. The number of labeled voxels was summed and multiplied by voxel dimensions to yield a total volume in cm^3. We obtained FLAIR data from individuals in Cohort 1 (Table 7) and performed this analysis on these 66 individuals.

Seed based analysis

We performed a seed based analysis using the regions described by Andrews hanna, et al.[62] in the 3 DMN subnetworks, namely: the Dorsomedial subsystem (DM): temporal pole, temporal parietal junction, lateral temporal cortex, dorsomedial prefrontal cortex; Medial temporal lobe subsystem (MTL): Hippocampal formation, parahippocampal cortex, retrosplenial cortex, posterior inferior parietal lobule, ventromedial prefrontal cortex; Midline core (MC): anterior medial prefrontal cortex, posterior cingulate and precuneus. We calculated measures of pairwise connectivity between each pair of regions, for a total of 56 measures of pairwise connectivity.

DMN WMH value

To obtain measures of DMN WMH across the subnetworks, we added together volumes across the subnetworks to obtain a volume of WMH for each subnetwork. For the MTL we included bilateral Hippocampal formation, parrahippocampal cortex, retrosplenial cortex, posterior inferior parietal lobule. For the MC we included the anterior medial prefrontal cortex and posterior cingulate and precuneus. For the DM subsystem we included temporal pole, temporal parietal junction, lateral temporal cortex, dorsomedial prefrontal cortex.

Statistical analysis

DMN WMH across races

To determine whether there was a difference between racial groups in DMN WMH volume, we constructed one multivariate linear model with the DMN WMH volumes as the outcome variable. Racial group was modeled as a fixed factor, and our covariates were age, gender, and APOE e4 status.

DMN WMH and connectivity

Because we previously identified racial differences in the relationships between connectivity and AD biomarkers for connectivity between the midline core and dorsomedial subsystems, we focused on these connectivity measures for the WMH analysis. We constructed linear regression models with our connectivity measures between the nodes of the midline core and dorsomedial subsystems as our outcome variables, and race and WMH volume as our independent variables of interest, while controlling for age, gender, and APOE status. Additionally, we constructed a race by diagnosis interaction term to determine whether the relationship between WMH and connectivity differed according to racial group.

To determine whether WMH within DMN nodes accounted for the racial differences that we identified in our previous work, we constructed Race X AD biomarker interaction terms (CSF Aβ42, CSF tau, and MoCA scores). We used these biomarker interaction as dependent variables, with the aforementioned covariates. We then included the three default mode WMH scores as independent variables to determine whether WMH accounted for racial differences we observed.

3.3 Results

DMN WMH across races

There was no significant difference between racial groups in WMH volume of the DMN subnetworks: DM(B=0.02, t(3,72)=1.24, p=0.22), MTL(B=0.004, t(3,72)=0.16, p=0.88), MC(b=0.02, t(3,73)=0.42, p=0.68). The only subnetwork that had a large proportion of individuals that did not have any WMH was the DM subnetwork. Chi-squared tests for distribution of WMH across races for this subnetwork were not significant.

DMN WMH and connectivity

In this re-analysis of the data, we were able to replicate one of our previous findings. There was a significant race x CSF Aβ42 interaction term for connectivity between the dorsomedial prefrontal cortex and the precuneus/posterior cingulate such that as CSF Aβ42 decreased, connectivity increased between these regions within AAs(B=-0.002, t(5,26)=-2.02, p=0.05). We were not able to replicate our previous findings according to CSF t-Tau and cognition (Table 6).

WMH volume within the specific regions of interest as well as within the midline core and dorsomedial subsystems was not related to our interaction terms. Because we had such a small number of regions for which the race X biomarker term was significantly relate to connectivity, we also included the dorsomedial prefrontal cortex and precuneus WMH volumes in our analysis. The inclusion of subsystem total WMH volumes within the MC, DM, and regional dorsomedial prefrontal cortex and precuneus WMH volumes into our model did not reduce the significance of the interaction term for the Aβ42 X Race interaction term.

3.4 Discussion

DMN white matter hyperintensity volumes were not significantly different between races, nor were there distributional differences between races. This indicates that the underlying cause of the disparate connectivity to biomarker relationships that we previously observed may not be the presence of WMH within these nodes. These findings lend credence to the hypothesis that WMH and Abeta have separate etiologies, but these findings should be considered with caution for the reason mentioned below. While we cannot say definitively that DMN WMH do not account for the observed differences in race to biomarker relationships, this preliminary data does suggest that the WMH in the DMN do not have a robust effect on connectivity. Other hypotheses about the nature of the disparities are that African American connectivity profiles may be different as a result of tau distribution, as African Americans have lower tau.

While understanding the mechanism behind functional connectivity disparities has significance for treatment interventions and disease etiology and progression, the lack of a clear mechanism in this body of work does not make it insignificant. It is important to rule out potential biological mechanisms that could explain health disparities before jumping to social explanations as the cause. In this case, WMH did not explain the disparate Aβ42 to connectivity relationships we observed in this cohort, and thus it will be appropriate to explore other biological mechanisms and social constructs, (i.e. cytokines[144] or perceived stress[124]) that exhibit disparities along racial lines.

It is difficult to transpose the findings from this analysis onto our previous results. This analysis was conducted in a separate, smaller cohort. We detected less significant race X biomarker interaction terms than our previous analyses. This is likely because this analysis is underpowered, and we did not have any AA individuals with AD in this cohort, which makes this particular sample non-representative of the AA with dementia population at-large. The lack of significant findings in this cohort should not be taken as evidence that WMH do not play a role in DMN connectivity, rather that our sample size was likely insufficient to detect a significant result, as previous studies with larger sample sizes have identified relationships between WMH and DMN connectivity in the context of AD[4,213,214]. An alternative explanation could be that WMH within the regions that we analyzed may not influence connectivity, and that other regions outside the DMN subnetworks may be influencing connectivity.

We conducted power analysis to determine how many people we would need to detect a significant effect given the effect size of our interaction terms. Using the "pwr" package in R. we determined that we would need a sample size of 118 to detect a significant effect, and our sample size of 66 falls short of this number. We are currently obtaining images from a larger set of both AA and NHW individuals with NC that also have FLAIR and fMRI data, and we plan to mine the large OASIS dataset that includes both cross sectional and longitudinal FLAIR and fMRI data of over 700 individuals, with more than 100 who self-identify as African American[215].

3.5 Chapter 3 tables

Table 4 Results from the replication analyses in the cohort for which we obtained regional WMH volume. N= 66. dmPFC = dorsomedial prefrontal cortex, PCC = precuneus and posterior cingulate, TC = lateral temporal cortex, TempP = temporal pole.

		B	t	p
dmPFC to PCC	Race X CSF Aβ42	**-0.002**	**-2.02**	**0.05**
	Race X CSF tau	0.004	0.88	0.39
	Race X Cognition	-0.03	-1.29	0.2
LTC to PCC	Race X CSF Aβ42	-0.0001	-0.2	0.84
	Race X CSF tau	-0.003	-0.74	0.5
	Race X Cognition	-0.02	-1.5	0.15
TemP to PCC	Race X CSF Aβ42	-0.001	-0.5	0.62
	Race X CSF tau	0.001	0.3	0.77
	Race X Cognition	-0.02	-1.6	0.11

The following manuscript was submitted for publication and is under review at Brain Connectivity. We have reprinted it here for the purposes of satisfying the dissertation requirements.

4   PUTAMEN CONNECTIVITY ALTERATIONS IN ALZHEIMER'S DISEASE

Misiura, M.B. [1,2,3], Igwe, K. [4,5], Wharton, W. [6], Tannahill, A. [1], Howell, J.C. [4,7], Verble, D.[6],

Zetterberg, H.[8,9,10,11], Kumar, V. [6], Kollhoff, A.[2], Willis-Parker, M. [2], Hu, W.T.* [2,7], Brickman, A.M.[4,5,12],

Turner, J.A.* [1,3]

[1]Psychology Department, Georgia State University, Atlanta, GA
[2] Neurology Department, Emory University, Atlanta, GA
[3] Tri-Institutional Center for Translational Research in Neuroimaging and Data Science, Georgia State University, Atlanta, GA
[4]Department of Neurology, Columbia University College of Physicians and Surgeons, New York City, New York
[5]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University College of Physicians and Surgeons, New York City, New York
[6] Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA
[7] Goizueta Alzheimer's Disease Research Center, Emory University, Atlanta, GA
[8]UK Dementia Research Institute at UCL, London, United Kingdom
[9]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom
[10]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
[11]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
[12]Gertrude H. Sergievsky Center, Columbia University College of Physicians and Surgeons, New York City, New York
*Official Co-corresponding authors: William T. Hu: william.hu@emory.edu & Jessica A. Turner:

jturner63@gsu.edu

Corresponding author for the purposes of communication from the journal about the manuscript: Maria

Misiura: mmisiura1@gsu.edu

Keyword terms: Alzheimer's Disease, Anterior putamen, white matter hyperintensities, cognition,

functional connectivity, frontal lobe

Abstract

Background: Pathologic and functional studies of Alzheimer's disease (AD) indicate fronto-putaminal networks as sources of neurological changes in response to disease. However, limited research has examined AD-associated changes in connectivity between the putamen and its supra- and infra-tentorial outputs, and of their relationships with measures of ischemic injury. In this study, we set out to determine how functional connectivity between the anterior putamen (APu) and other brain regions relates to AD and regional white matter hyperintensity (WMH) volume. Because we previously identified disparate default mode network connectivity patterns between Black/African American (AA) and non-Hispanic white (NHW) individuals according to AD, we also analyzed the impact of race on putamen-related connectivity.

Methods: In our sample of 267 individuals with normal cognition, mild cognitive impairment, and AD dementia, we measured functional connectivity between APu and multiple cortical regions. We then modeled the relationships between AD-associated features (cognition, CSF AD biomarker levels), regional WMH, APu-connectivity, and race.

Results: Measures of AD (diagnosis, worse cognition, and decreased CSF Aβ42) were associated with increased connectivity between the APu and pre-/post- central gyrus in both races. At the same time, race modified the relationship between connectivity and measures of AD between the APu and superior/middle frontal gyri. Frontal and putaminal WMH also had more negative impact on the connectivity between APu and superior/middle frontal gyri in AA, even though WMH in the same regions had the opposite effects in NHW.

Discussion: In this manuscript we argue three points: 1) AD alters connectivity between APu and its input (pre/post central gyrus) independent of race, 2) these changes extend to the superior and middle frontal gyrus in AAs, and 3) biomarkers of AD and WMH each exerted race-dependent influence on APu connectivity with the superior/middle frontal gyrus.

Impact statement: This is the first study to specifically probe the APu-related connectivity according to AD and regional WMH volume. Similar to our prior observations in the default mode

network, APu connectivity to other brain regions is sensitive to race in some paths, yet independent of race in others. These extend our previous finding that AD and vascular biomarkers are associated with differential – and sometimes opposite – functional consequences in AA and NHW.

Acronyms: APu= anterior putamen, NC= normal cognition, AD= Alzheimer's Disease, WMH= White matter hyperintensities, AA= African American, NHW= non-Hispanic white, DMN = Default mode network

4.1 Introduction

While often overlooked in studies of Alzheimer's disease (AD) research – including histological studies, PET, and structural neuroimaging – has shown the putamen and frontal lobe to be vulnerable to AD pathology as well as ischemic damage. The striatum, which includes the caudate and putamen, may exhibit amyloid deposition and AD-related atrophy as much as 10 years before symptom onset in individuals at risk for AD[154, 215,216]. Similarly, neuritic plaques as well as neurofibrillary tangles begin to appear in the frontal lobe in early and intermediate stages of AD[217,218]. The appearance of these pathologic lesions in AD has further been linked to neuronal dysfunctions through FDG-PET studies[219,171,220,221] and MRI volumetric analysis[77]with the putamen much more affected by AD than the functionally-related and spatially adjacent caudate. Therefore, an improved understanding of the putamen's role in aging and early AD can provide a novel region for biomarker development and a potential target for clinical intervention studies.

Functional connectivity is a widely used method for understanding disease related neurological changes. Functional connectivity is defined as a measure of the synchronicity of blood-oxygen level dependent (BOLD) signal between brain regions, typically collected during a resting-state functional magnetic resonance imaging scan [222]. Within AD, the most studied regions lie within the default mode network (DMN) [223]. There exist scientific rationale and precedent for examining the impact of AD on DMN [224], yet other local and large-scale brain connections are often overlooked [223]. The functional networks of the putamen are well-defined in neuroscience due to their importance in movement regulation and disease. Within the frontal lobe, the putamen is most structurally connected to the superior and middle frontal gyri, and pre and post central gyri[86,126,108,225]. These areas are thought to work together to meet visual spatial and motor demands[226,227]. The anterior putamen (APu) is classically viewed as a an associative region while the posterior putamen supports motor function [87]. The APu is also more affected by AD than its posterior counterpart in structural MRI[88–90] and better correlates with cognitive decline[91].

Because putamen's connectivity with other brain regions is also most consistent across individuals among basal ganglia structures[86], the APu is a logical focus of our investigation in AD.

Consistent with this, limited evidence exists to implicate frontal-APu connectivity in AD[228–230], but the opposite has also been reported[231]. One caveat may be the presence of striatal – more specifically, putaminal – white matter hyperintensity (WMH) which is commonly observed in older individuals including those with AD [232]. WMH has been linked to strokes and cerebrovascular risk factors (e.g., diabetes), [93] but also neuro-inflammation [233]. While there is agreement that total brain WMH volume is a risk factor for AD but is not a specific marker for AD, [234], it remains controversial whether WMH has uniform etiology or impact on cognition across the brain. Region-specific WMH quantification implicates vascular disease to associate with amyloid deposition for posterior portion of periventricular WMH changes [94]. However, recent evidence indicates that WMH could emerge independently of vascular disease and arise as a direct inflammatory response to neuritic plaques in AD[103,235].

Relevant to our APu connectivity analysis, WMH can disrupt BOLD synchronicity between brain regions [236]. Decoupling of functional and structural connectivity increases as WMH burden increases on a global [236] and tract-specific scale[108]. In AD, regions of the DMN show decreased connectivity if the WM tracts connecting them have a high WMH burden[166]. Furthermore, WMH load in one WM tract can affect functional connectivity between nodes along a separate tract, suggesting direct and indirect impact on functional connections[118]. Regional distribution differences in WMH may generate unique functional network and therefore cognitive profiles that cannot be parsed apart by using total WMH volume. WMH typically correlate with tests of speed and executive function, and not with tests of fluid or crystallized intelligence[102,237]. This suggests that their presence may disrupt intracerebral brain connectivity, as tests of executive function rely on a coordinated effort of multiple brain regions to perform tasks [238]. Due to their vascular origin and role in brain connectivity, regional WMH differences may explain many of the functional connectivity changes observed in aging and dementia.

Like other AD biomarker studies, brain network analysis should examine potential differences between racial groups to test generalizability. Independent of whether self-reported race reflects genetic

similarity according to region of ancestry, identification with an ethno-cultural group, or structural racism, there are real and observable biological outcomes from racial disparities which need to be measured [200]. This is particularly true for studies of AD as African Americans (AA) are approximately twice as likely to develop AD in their lifetime as non-Hispanic whites (NHW), and are more likely to have existing comorbidities such as vascular disease and type-2 diabetes[121,239,240]. In keeping with AD biomarker differences between races, our previous DMN analysis showed disparate relationships between functional connectivity and AD biomarkers according to race [211]. Specifically, AA individuals exhibited increased connectivity between two tau-related DMN subsystems as disease burden increased. CSF studies have also shown African American individuals exhibit a unique tau – but not amyloid or neurofilament light chain – biomarker profiles[15,241]. Given the complexity between AD, WMH, and race, here we present a study of APu connectivity in AA and NHW participants using three diverse cohorts recruited from the Atlanta area.

4.2 Methods

Data collection for all studies, including re-analysis of existing data were approved by the Emory University and Georgia State University Institutional review board.

Participants

Our analyses consisted of three cohorts of previously collected data from three studies. Separate tables for each cohort are included in the supplemental materials. Cohorts 1 and 2 (N=66 and 113; PI: Hu) recruited individuals over the age of 65 including individuals with normal cognition (NC), mild cognitive impairment (MCI), and AD dementia. Cohort 3 (N=88, PI Wharton) was designed as a study of cardiovascular risk factors for dementia among African American women with normal cognition. Each participant underwent a detailed interview for demographic information, self-reported race (Caucasians of Hispanic or Latino ethnicity were not included in this study), vascular risk factors (coronary artery disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes, suspected transient ischemic attack), other medical comorbidities (e.g., cancer), and medications (e.g., use of

angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers). Each participant was then assigned a diagnosis according to consensus criteria including those for NC, MCI, and AD dementia (global Clinical Dementia Rating of 1 or 2.) Cognitively impaired subjects suspected of having a non-AD dementia (vascular, Lewy body, and frontotemporal dementia) were excluded.

For Cohort 3, middle-aged African American and Caucasian subjects were recruited into a study of cognitively normal subjects with a family history of AD dementia. Demographic (age, sex, education), diagnostic (syndrome, global Clinical Dementia Rating [CDR], Mini-Mental State Examination [MMSE]) and *APOE* allelic information were collected. Table 1 includes the demographic information across cohorts, and table 2 includes demographic information stratified by cohort. Total number of individuals with NC=187, MCI=53, AD=27.

MRI data collection

All participants were scanned on a Siemens 3T MRI machine at the Emory Center for Systems Imaging with scanning protocols for each cohort included below.

Cohort 1

Scanning protocol included a T1-weighted 3D MPRAGE sequence (TR/TI/TE = 2400/1060/2.31msec, flip angle = 8°, matrix =320x300, and voxel size = $0.8 \times 0.8 \times 0.8 mm^3$) and a 6 minute eyes-open resting state functional MRI scan (TR/TE = 724ms/32ms flip angle = 52°, field of view (FOV) = 220×220 mm^2, acquisition matrix = 104×104, voxel size = $2 \times 2 \times 2$ mm^3, slice = 91, time point = 550), and a T2-weighted Fluid attenuated inversion recovery (FLAIR) can (TR/TI/TE = 9000/2500/91 msec, flip angle = 150°, matrix =256x256, and voxel size = $0.8 \times 0.8 x5mm^3$).s

Cohort 2

Scanning protocol included a T1-weighted 3D MPRAGE sequence (TR/TI/TE = 1620/950/3msec, flip angle = 30°, matrix = $192 \times 256 \times 160$, and voxel size = $0.98 \times 0.98 \times 1mm^3$) and a 6 minute eyes-open resting state functional MRI scan (TR/TE = 3000ms/32ms flip angle = 90°, field of

view (FOV) = 200 × 200 mm^2, acquisition matrix = 64 × 64, voxel size = 3.1 × 3.1 × 3.5 mm^3, slice = 33, time point = 124).

Cohort 3

Scanning protocol included a T1-weighted 3D MPRAGE sequence (TR/TI/TE = 2300/800/2.89msec flip angle = 8º, matrix =256 x256x176, and voxel size = 1×1×1mm$^{3)}$ and a 4.25 minute eyes-open resting state functional MRI scan (TR/TE = 3000ms/32ms flip angle = 90º, field of view (FOV) = 200 × 200 mm^2, acquisition matrix = 220 × 220 x 144, voxel size = 2 x 2 x 2 mm^3, slice = 48, time point = 170).

MRI Data preprocessing

We conducted preprocessing pipelines with identical procedures for each cohort. To control for the difference in scanning parameters, we included cohort as a fixed effect in our statistical models. We utilized a standard preprocessing pipeline utilizing the DPARSFA toolbox [172]. The first 10 timepoints were removed, scans were slice time corrected, manually re-oriented, realigned, normalized and smoothed using the DARTEL & algorithm [213]. This algorithm is more appropriate than standard normalization to the MNI template for special populations, such as those with atrophy. We then performed nuisance covariate regression (Friston's 24 parameter head motion regressors, CSF, WM). We further removed motion-confounds using ICA-AROMA [242] and applied a high pass filter.

Neuropsychological testing

Each cohort utilized a different cognitive battery or test. Data collection for cohort 1 utilized a cognitive battery as previously described [15]. Briefly, this battery included memory tests (Consortium to Establish A Registry for Alzheimer's Disease word list delayed recall, Brief Visual Memory Test–Revised [BVMT-R] delayed recall), (2) executive function tests (Trail Making Test B, reverse digit span [RD], Symbol Digit Substitution Test, and letter-guided fluency), (3) language tests (Boston Naming Test [60 items], category fluency), and (4) visuospatial function tests (Judgment of Line Orientation[JOLO], Rey-Osterrieth complex figure test). With the exception of BVMT-R, JOLO, and RD, subtest Z-scores were calculated according to published normative data, adjusting for age, sex, education, and race. Z-

scores for the four domains were averaged to generate composite cognitive Z-scores. Neuropsychological data collection for cohort 2 included administration of the Montreal Cognitive assessment (MoCA). Data collection for cohort 3 included administration of the mini-mental state exam (MMSE). To control for the variety of scales and neuropsychological assessments between cohorts, we z-scored the data from cohorts 2 and 3 according to race, and controlled for cohort in our statistical analysis. In out statistical analyses, cognitive scores were multiplied by negative one so that an increasing score indicates declining cognitive performance.

CSF collection

CSF (20 mL) was collected using protocols modified from the Alzheimer's Disease Neuroimaging Initiative (ADNI) using 24G Sprotte atraumatic needles and syringe between 8AM and noon without overnight fasting, and transferred into two 15 mL polypropylene tubes. For the Emory cohort 3, CSF was centrifuged at 2,000 rpm for cellular studies; the supernatant was removed, immediately aliquoted (500 μL), labelled, and frozen (−80 °C) until analysis. Because CSF-tau is typically lower in African Americans [243], and tau related changes typically emerge after amyloid deposition (low CSF Aβ42) [244], we z scored CSF t-tau according to race, and only analyzed CSF t-tau within individuals with an amyloid z-score of less than 1. We multiplied CSF Aβ42 by -1 so that increasing amyloid levels indicate increasing amyloid burden.

Area deprivation index

To control for socioeconomic status, we utilized the online neighborhood atlas developed at the University of Wisconsin, Madison (https://www.neighborhoodatlas.medicine.wisc.edu/). Using participant addresses, we obtained area deprivation index scores.
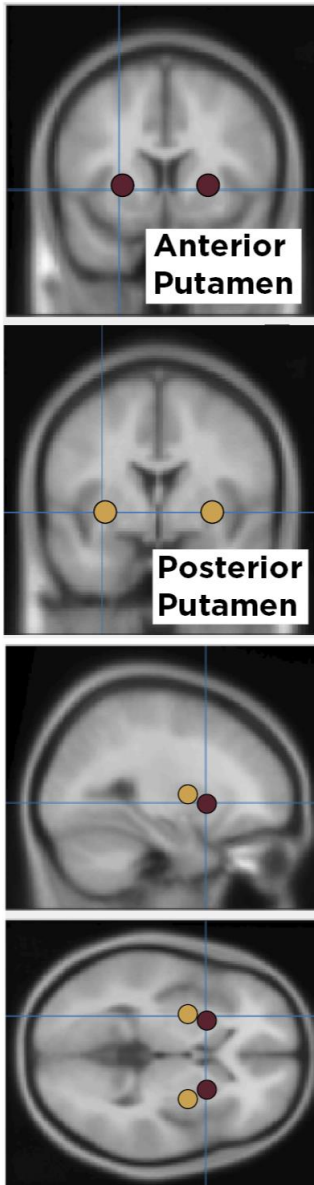
Figure 7 Cross sectional images of the empirically defined anterior and posterior putamen seeds.

Seed Based Analysis

Using the Wake Forest University Pickatlas v3.0.5, we created an anterior and posterior putamen mask by creating a 9mm sphere around the center of the APu, and center of the posterior putamen in MNI space using coordinates outlined by Oberhuber et al., 2013, for each hemisphere (Yin et al., 2009. Frontal regions highly connected to the putamen, as determined by human tractography studies, include the superior frontal gyrus, precentral gyrus, middle frontal gyrus, postcentral gyrus (Cacciola et al., 2017). Additionally, the putamen is a highly lateralized region with strong ipsilateral connections (Cacciola et al., 2017). As such, we only considered connectivity values between ipsilateral nodes.

We calculated seed to seed functional connectivity using the DPARSF-A toolbox. Using our own anterior and posterior putamen seeds and masks of the aforementioned regions as defined by the Automated Anatomical labeling atlas, we calculated connectivity between the putamen and these regions (Table 3).
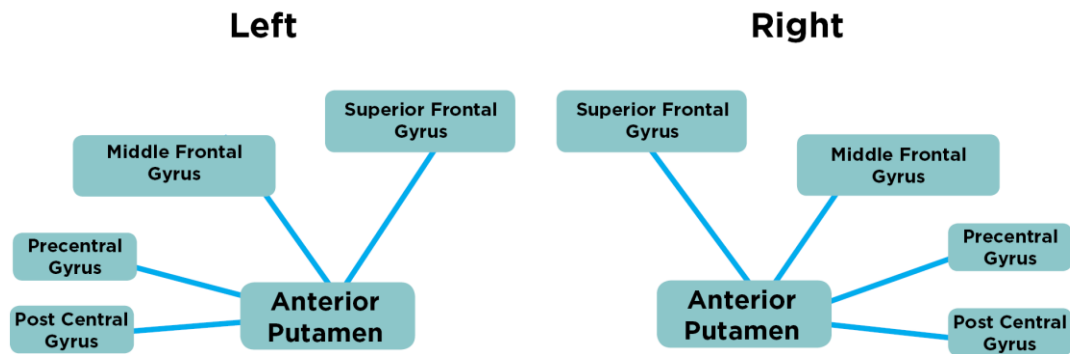
Figure 8 Visual representation of the connectivity measures used in this analysis. Supplemental figures include a 3-D representation of the seed maps.

Regional white matter hyperintensity volumes

Total WMH volumes were derived from T2-weighted fluid-attenuated inversion recovery images software developed by researchers in the Brickman Lab at Columbia University [214]. Briefly, each participant's fluid-attenuated inversion recovery image was corrected for intensity normalization, then skull-stripped and intensity normalized again. The skull-stripped images were sent through a high pass filter at the mode of the distribution of the image voxel intensity values. A half Gaussian mixture model was fit to the log-transformed histogram of the intensity values of each image. The Gaussian distribution that encapsulated the highest intensity values defined the hyperintense voxels and was labeled. Any cluster of labeled voxels that comprised fewer than five voxels was removed from the mask. The labeled images were visually inspected and false positives removed. The number of labeled voxels was summed and multiplied by voxel dimensions to yield a total volume in cm^3. We obtained FLAIR data from individuals in Cohort 1 and performed this analysis on these 66 individuals.

Regional WMH load

Because we had many people that did not have a WMH in either the putamen or frontal nodes, rather than analyze the continuous volumes, we created scores that reflected whether a WMH volume was present in a particular region. To create regional WMH load, we coded volumes as 0 for not present in either the putamen or nodes in the analysis (pre and post central gyrus 1 for present in either putamen or sensorimotor nodes, and 2 for present in both putamen and sensorimotor nodes. We created a similar score using the same procedure for frontal nodes including the middle and superior frontal gyrus.

Statistical analysis

Anterior putamen connectivity and Alzheimer's Disease Burden

Diagnostic categories

We created two multivariate linear regression models (one for each hemisphere) that included the 8 pairwise measures of connectivity as dependent variables, self-reported race, gender, cohort, presence of hypertension and type-2 diabetes, and APOE ε4 carrier status as fixed factors, and age, area deprivation index, and mean frame-wise displacement as covariates. Diagnostic category was included as a fixed factor. We corrected for multiple comparisons using the Holm FWER correction method.

AD biomarkers

Next, we analyzed whether AD related biomarkers corresponded with observed connectivity changes. To further determine which disease biomarkers may be related to connectivity, we constructed models that did not include diagnosis, and instead included CSF t-tau, CSF Aβ42, cognitive scores, and putamen-frontal WMH scores, with the same covariates. We corrected for multiple comparisons using the Holm FWER correction method. To maintain consistency in presentation of our results, cognitive scores and CSF Aβ42 were inversed such that in our analyses and results, an increasing cognitive score indicates worse cognitive performance (greater cognitive impairment), and increasing CSF Aβ42 indicates increasing amyloid burden (lower CSF Aβ42).

Racial differences in frontal to anterior putamen connectivity

Racial differences in normal cognition

To establish underlying racial differences, we constructed two multivariate linear regression models (one for each hemisphere) that included the 8 pairwise measures of connectivity as dependent variables, self-reported race, gender, cohort, APOE ε4 carrier status, and presence of hypertension and type-2 diabetes as fixed factors, and age, area deprivation index, and mean frame-wise displacement as covariates. We corrected for multiple comparisons using the Holm FWER correction method. To maintain consistency in presentation of our results, cognitive scores and CSF Aβ42 were inversed such that in our analyses and results, an increasing cognitive score indicates worse cognitive performance (greater cognitive impairment), and increasing CSF Aβ42 indicates increasing amyloid burden (lower CSF Aβ42).

White matter hyperintensities and connectivity

We next wanted to establish whether there were regional differences between NHWs and AAs in individuals with mild cognitive impairment within and between the nodes of our fronto-putamen network, basal ganglia, and the default mode network. We did this using two methods; 1) Performed a chi-squared test to determine whether the distribution of WMH fronto-putamen scores was different according to race 2) created a multivariate linear regression model that controlled for age, gender, and APOE ε4 status, and hypertension to determine whether WMH volume was significantly different between races within individuals with normal cognition.

We also wanted to determine whether CSF Aβ42 was related to putamen frontal WMH load. In this linear model, CSF Aβ42 was the outcome variable. We controlled for age, gender, race, APOE ε4, and hypertension.

Racial Differences in AD burden to connectivity relationships

We next analyzed whether race modified biomarkers to connectivity relationships by constructing two linear mixed models that included diagnosis, CSF t-tau, CSF Aβ42, cognitive z-scores, and putamen frontal WMH scores and the following interaction terms: race X diagnosis, race X CSF t-Tau, race X CSF Aβ42 burden, Race X Cognitive impairment, and race X fronto-putamen WMH load. We included the 8 pairwise measures of connectivity as dependent variables, self-reported race, gender, cohort, APOE ε4

carrier status, and presence of hypertension and type-2 diabetes as fixed factors, with age, area

deprivation index, and mean frame-wise displacement as covariates. We corrected for multiple

comparisons using the Holm FWER correction method. To maintain consistency in presentation of our

results, cognitive scores and CSF amyloid were inversed such that in our analyses and results, an

increasing cognitive score indicates worse cognitive performance (greater cognitive impairment), and

increasing CSF Aβ42 indicates increasing amyloid burden (lower CSF Aβ42).

4.3 Results

Regions of interest

We initially included separate ipsilateral nodes between the APu and the posterior putamen,

caudate, insula, precentral gyrus, postcentral gyrus, middle frontal gyrus, and superior frontal gyrus, as

these regions are the most structurally connected to the putamen (Cacciola, et. al, 2017). In our initial

analyses, cognition and diagnosis were not significantly related to connectivity between the APu and the

posterior putamen, caudate, and insula, and exhibited no racial differences in individuals with NC. Thus,

we report here our analyses for connectivity measures between Apu and the following regions; pre and

post central gyri, and middle and superior frontal gyri for the remainder of the results.

APu connectivity and AD features

Diagnostic categories

After controlling for age, sex, race, and APOE ε4, connectivity between the right APu and the

right precentral gyrus was significantly different among diagnostic categories (precentral: β=0.13,

$t(7,255)=1.65$, $p=0.05$; postcentral: β=0.14, $t(2,255)=1.79$, $p=0.05$). Individuals with AD had significantly

greater connectivity than individuals with NC and MCI between the right APu and the right precentral.

(Table 3)

Cognitive impairment

Connectivity between the right APu and pre and post central gyrus correlated with cognitive

impairment such that as amyloid burden increased, connectivity also increased (pre-central gyrus: β=0.04,

$t(6,251)=1.70$, $p=0.04$; postcentral gyrus: $\beta=0.05$, $t(6,251)=2.21$, $p=0.03$) (Figure 3A). There was no such finding in the left hemisphere. (Table 3)

CSF biomarkers

Connectivity between the left APu and cortical regions correlated with Aβ42 burden (precentral gyrus: $\beta=0.05$, $t(6,174)=1.76$, $p=0.04$; postcentral gyrus: $\beta=0.05$, $t(6,174)=1.68$, $p=0.05$) (Figure 3B). CSF t-Tau was not significantly related to any of our connectivity measures of interest. Model results are included in the appendix.

Regional WMH load

WMH load within pre and post central gyri and putamen was related to connectivity between the right and left APu and the respective pre and post central gyri. In the right hemisphere, as WMH load increased, precentral ($\beta=-0.16$, $t(6,55)=-2.02$, $p=0.04$) and postcentral($\beta=-0.18$, $t(6.55)=-2.43$, $p=0.01$) gyrus connectivity decreased, and in the left hemisphere, precentral ($\beta=0.09$, $t(6,55)=2.04$, $p=0.04$) gyrus connectivity increased (Figure 3D). Neither Regional WMH load was significantly related to CSF Aβ42, and when CSF Aβ42 was included in the WMH models, beta coefficients for functional connectivity values did not significantly change. Model results are included in the appendix.

Figure 9 Race independent connectivity to biomarker relationships. A) Amyloid and functional connectivity in the left hemisphere between the Apu and the pre and post central gyri.. Line color indicates region. B) Amyloid burden and functional connectivity in the right hemisphere between the Apu and pre and post central gyri. Line color indicates region. C) Regional WMH load and functional connectivity in the left hemisphere in cohort 2. Line color indicates region. D) Regional WMH load and functional connectivity in cohort 1 in the right hemisphere. Line color indicates region. Grey background indicates a 95% CI. E) Summary figure of race independent relationships. AA = African American, NC = normal cognition, WMH= white matter hyperintensities.

Racial differences in putamen connectivity

Racial differences in individuals with normal cognition

Within controls, African Americans had significantly lower connectivity than NHWs between the left APu and the left superior frontal (β=0.11, t(5,177)=2.10, p=0.04), left precentral gyrus (β=0.14, t(5,177)=2.31, p=0.02), left middle frontal gyrus(β=0.14, t(5,177)=2.79, p=0.01). In the right hemisphere, African Americans had significantly lower connectivity than NHWs between the right APu and the right middle frontal (β=0.16, t(6,167)=2.60, p=0.01), and right superior frontal(β=0.15, t(6,167)=2.54, p=0.01). The presence of type-2 diabetes, and hypertension, and area deprivation index scores did not account for the effect of race on connectivity. Model results are included in table 3.

Racial differences in amyloid beta and fronto-putamen connectivity

Race significantly modified the relationship between Aβ42 and connectivity between the left APu and left middle frontal gyrus (β=-0.12, t(7, 172)=-2.25, p=0.02), and the between the right APu and right middle frontal gyrus (β=-0.20, t(7,172)=-3.30, p=0.001) and the right superior frontal gyrus (β=-0.16, t(7,172)= -2.36, p=0.02) such that within African Americans, as amyloid burden increased, connectivity decreased (Figure 4A). Model results are included in the supplemental table.

Racial differences in regional WMH load and functional connectivity

Race significantly modified the relationship between WMH load in the putamen, superior frontal, and middle frontal gyri and connectivity between the left APu and superior frontal gyrus (β=0.18, t(6,55)=2.34, p=0.02), and middle frontal gyrus (β=0.16, t(6,55)=1.98, =0.04) (Figure 4B). Model results are included in the supplemental table.

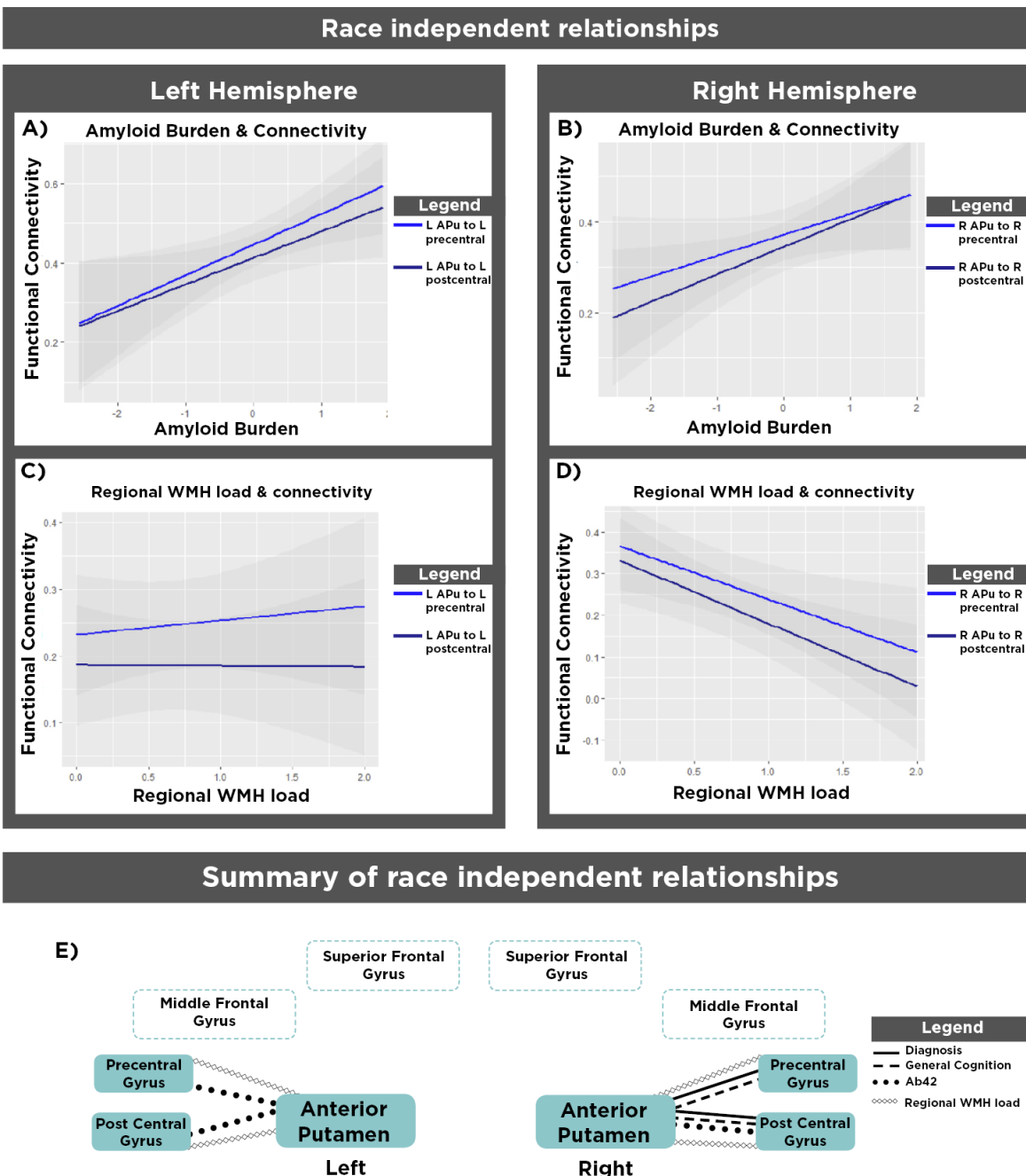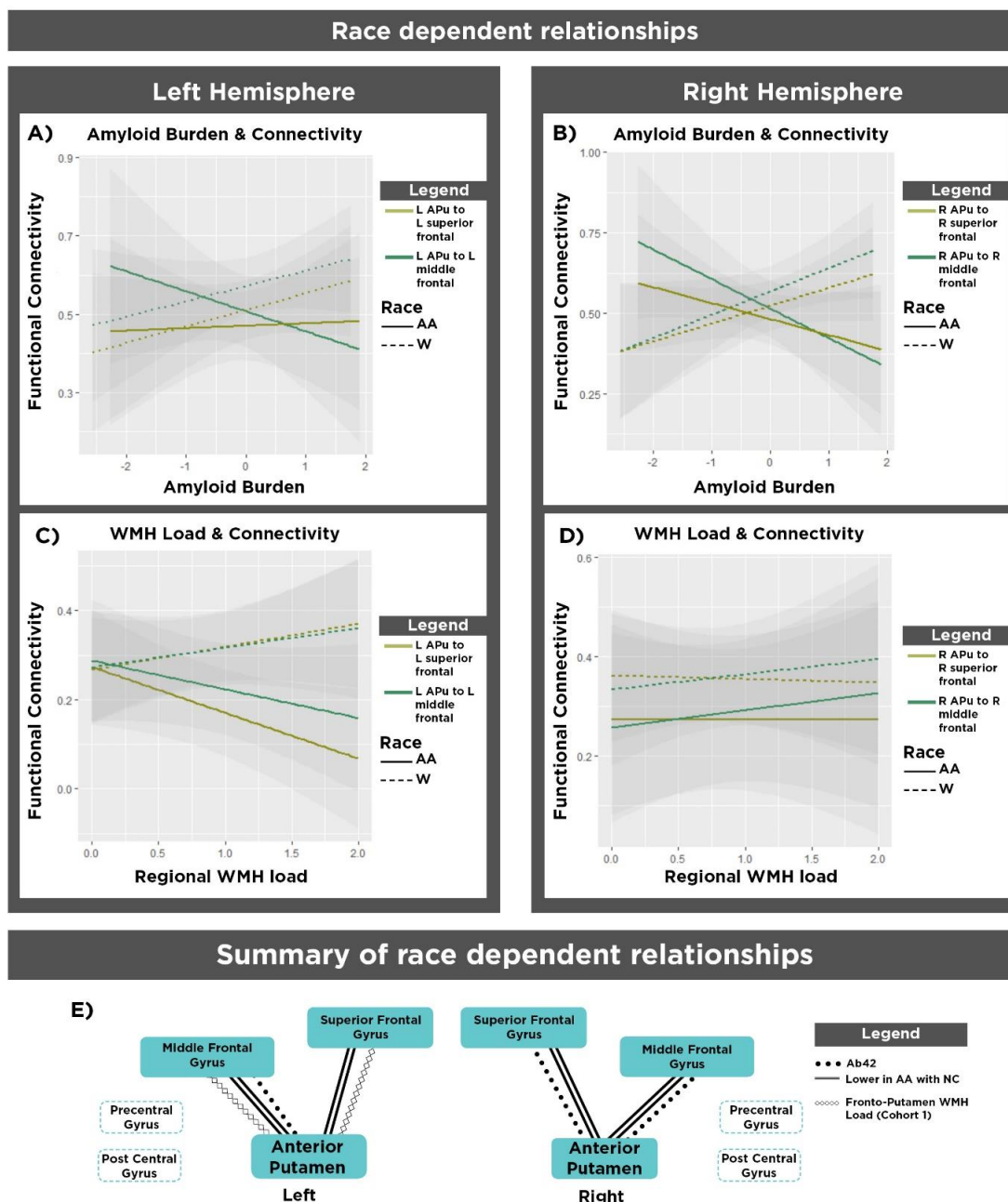Figure 100 Race dependent connectivity to biomarker relationships. A) Amyloid burden and functional connectivity in the left hemisphere between the Apu and superior and middle frontal gyri. Line color indicates region. Dashed line indicates race, solid line indicates NHW. B) Amyloid burden and functional connectivity in the right hemisphere between the Apu and superior and middle frontal gyri. Solid line indicates African American, dashed line indicates NHW. Grey background indicates a 95% CI. C) Regional WMH load in the left hemisphere between the middle and superior frontal gyri. Line colors indicates regions, Solid line indicates African American, dashed line indicates NHW. D) Regional WMH load in the right hemisphere between the middle and superior frontal gyri. Line colors indicates regions, Solid line indicates African American, dashed line indicates NHW. E) Summary figure of race dependent relationships. AA = African American, NC = normal cognition, WMH= white matter hyperintensities.

4.4 Discussion

In this study, we found that fronto-putaminal functional connectivity is independently associated with AD and WMH. Connectivity between APu and its cortical inputs (pre-/post-central gyrus) were related to clinical and biochemical markers of AD. Effects of AD further extended to connections linking APu with its cortical outputs (superior/middle frontal gyrus) only in African Americans, with opposite relationships between WMH and connectivity in these regions between African Americans and NHWs. These findings are consistent with our previous report that African Americans and NHWs may show opposite patterns of brain connectivity change in parts of the brain but not others.

Prior studies have highlighted altered white matter track integrity between the putamen and its cortical inputs (post and pre central gyri) or outputs (middle and superior frontal gyri) (Purves, D et al., 2001) in dementia. Within vascular dementia, the putamen exhibits atrophy and impaired white matter tract integrity [232]. In early stages of AD (e.g., subjective cognitive complaints and mild cognitive impairment stages), the putamen and frontal lobe also exhibit impaired white matter integrity which correlates with increased amyloid burden[101,248] and decreased regional cerebral blood flow [249]. One may thus expect APu-related connectivity to decrease over time, consistent with current models of decreased DMN connectivity in AD[66,150 211]. However, DMN connectivity includes both long and short range brain connections and is a conglomeration of multiple white matter tracts [250]. If networks simplify in the presence of disease, connectivity between nodes may actually increase[198]. Indeed, we previously observed increased connectivity in certain parts of the DMN among African Americans with AD [211]. In the current work, increased connectivity between the APu and pre/post-central gyrus with more pathologic CSF Aβ42 for both races may also exemplify this phenomenon. Thus we do not interpret this increase in cortical input to APu as strictly pathological or compensatory at this time. It is therefore not straightforward to reconcile our findings with white matter tract analysis.

We also used a novel method to quantify WMH in the APu and its cortical connections impacted in AD. WMH is found commonly in AD and vascular dementia, and their presence in those with vascular risk factors but no neurological symptoms further complicates their interpretation in

neurodegeneration[102,103,251]. A region-specific approach to WMH analysis may better identify the pathologic process in that anatomical context, but regional analysis has broadly included qualitative or semi-quantitative distinction between deep vs peri-ventricular, anterior vs posterior, cortical vs. subcortical, and lobar vs. Brodmann area[102,250]. Building on the APu connectome, we were able to directly test whether WMH at APu network nodes influenced the inter-nodal connectivity within and across individuals. In this case, a negative association between nodal WMH and inter-nodal connectivity (e.g., right Apu-pre/post-central gyrus) supports the pathological role of nodal WMH, but a lack of association (e.g., right APu-superior/middle frontal gyrus) does not rule out the importance of WM tract abnormality. Importantly, the distinct effects of greater plaque burden (more pathologic CSF Aβ42) and WMH on all but one APu-related connectivity examined do not suggest WMH in the APu network to reflect AD-related pathology, even if posterior peri-ventricular WMH has been found to more associate with AD pathology than anterior peri-ventricular WMH.

APu-superior/middle frontal gyrus connectivity was the one measure which differed between African Americans and NHW. The left APu-cortical connectivity also showed the same direction of change between AD and WMH in African Americans. Although our analyses did not reveal a mechanistic explanation for the underlying connectivity differences, as connectivity values were not related to hypertension, presence of type-2 diabetes, or socioeconomic status, the magnitude and consistency of regions across hemispheres in which African Americans exhibited lower connectivity should not be discounted. Potential explanations of the underlying connectivity differences include dietary and lifestyle habits, brain-specific inflammatory responses [146], environmental and other exposure associated with poverty [252] and stress associated with social and racial inequity [207]. In animal and human neuroimaging studies, stress does seem to exert regional influence on fronto-striatal circuitry, particularly the middle and superior frontal gyri[253–255]. The stress of perceived racism, and additional relevant biological and environmental disparities that exist within the African American population could predispose these regions to AD pathology, but more research on life stressors would be necessary to draw this conclusion[126,256]. It is well recognized that standard predictors of disease progression such as

cognitive function and hippocampal volumes fall short in determining the rates of cognitive decline in African Americans[113]. Limited multi-racial studies have suggested WMH to better track dementia progression in African Americans than in NHW[113], yet many studies continue to exclude individuals with vascular disease or under-recruit minorities including African Americans. This study reiterates the importance of including individuals with vascular disease in AD research, especially those with greater prevalence of vascular disease as well as greater incidence of dementia.

This study has a number of limitations. We recruited more participants with NC and MCI than AD dementia, thus focusing our work on brain changes in older individuals without severe impairment at the expense of generalizability. Future research with increased AD dementia participants as well as longitudinal changes in WMH and AD pathology is necessary to validate the patterns we described. The cognitive measures utilized were not consistent across cohorts. Although Z-transformation controlling for cohort effect did yield significant connectivity-to-cognition relationships, casting a more extensive neuropsychological battery across all cohorts would extend the region-specific analysis to also cognitive functions. Amyloid and tau PET imaging was not performed in these subjects. Even though CSF Aβ42 levels closely correlate with global amyloid PET measures, the latter may provide higher resolution characterization of AD pathology in a region-specific manner[257].

Conclusion

In this study, we intended to determine whether AD affected putaminal connectivity. We identified the pre and post central gyrus within a network vulnerable to AD independent of race, and the superior and middle frontal gyrus within a related network displaying race-specific associations with AD. Connectivity was increased or showed no change in AD among NHW participants, but decreased more often than increased in African Americans.

These findings along with our previous work highlight that functional connectivity, like other intermediate measures of neurodegeneration, is not a linear metric of AD pathology or WMH. It provides a dynamic profile of neurodegeneration, and region- and context-specific changes likely have pathologic correlates which need more detailed confirmation. AD pathology appears to have a more consistent

connectivity profile between APu and its cortical inputs across races, with AD and WMH demonstrating different patterns of interaction between older African American and NHW participants. This work is in line with previous research recommendations that considering amyloid, tau, or cognitive decline without WMH is insufficient for a functional profile of older individuals, yet treating WMH as a uniform measure of either AD or vascular disease according to qualitative divisions (e.g., anterior vs. posterior) likely undermines its pathologic significance. Future experimental studies should focus on elucidating pathologic substrates which can selectively increase or decrease connectivity involving that region, and connectivity measures in these areas simultaneously vulnerable to AD, vascular injury, and neuro-inflammation can then be used to identify the WMH etiologies.

4.5   Chapter 4 Tables

Table 5 Combined demographic variables for all participants across cohorts. SD = standard deviation. M= male, F= female. MCI = mild cognitive impairment, AD = Alzheimer's disease.

	Normal Cognition (N=187)		MCI (N=53)		AD (N=27)	
	AA (n=95)	NHW (n=92)	AA (n=27)	NHW (n=26)	AA (n=8)	NHW (n=19)
Age mean(SD)	62.96 (9.29)	65.65 (9.15)	69.38 (7.88)	72.06 (6.36)	70.13 (10.34)	68.86 (8.63)
Gender %M/%F	21.05/78.95	45.65/54.35	44.44/55.56	46.15/53.85	37.50/62.50	47.37/52.63
National Area Deprivation Index mean(SD)	50.83 (24.10)	33.12 (21.99)	51.69 (23.18)	32.12 (20.73)	59.83 (32.08)	35.38 (21.71)
State Area Deprivation Index mean(SD)	4.40 (2.56)	2.85 (2.10)	4.38 (2.53)	2.28 (1.49)	5.67 (3.27)	2.94 (1.73)
Hypertension % have	50.53	34.78	77.78	57.69	75.00	31.58
Type-2 Diabetes % have	10.53	4.35	22.22	15.38	25.00	21.05
Cognitive Z score Mean (SD)	0.05 (0.92)	0.14 (0.81)	-0.66 (0.58)	-0.87 (0.80)	-2.26 (1.12)	-2.26 (0.70)

Table 6 Demographics stratified by cohort. AA = African American, NHW = Non-Hispanic White, SD = Standard Deviation.

	Cohort 1 (N=66)		Cohort 2 (N=113)		Cohort 3 (N=88)	
	AA (n=24)	NHW (n=42)	AA (n=52)	NHW (n=36)	AA (n=54)	NHW (n=59)
Age mean(SD)	69.27 (7.82)	70.03 (6.57)	58.49 (8.34)	58.58 (6.55)	68.92 (7.68)	71.00 (7.87)
Gender %M/%F	25.00/75.00	45.24/54.76	15.09/84.91	50.00/50.00	39.62/60.38	44.07/55.93
National Area Deprivation Index mean(SD)	47.83 (23.85)	27.95 (19.25)	53.19 (21.17)	37.11 (23.19)	51.35 (27.47)	34.65 (21.79)
State Area Deprivation Index mean(SD)	4.13 (2.52)	2.26 (1.43)	4.60 (2.24)	3.22 (2.26)	4.48 (2.97)	2.82 (2.04)
Hypertension % with it	62.50	30.95	43.40	33.33	69.81	47.46
Type-2 Diabetes % with it	20.83	7.14	3.77	0	20.75	15.25
Cognitive Z score Mean (SD)	-0.06 (1.15)	-0.08 (1.02)	0.07 (0.99)	0.02 (1.02)	-0.66 (0.94)	-0.87 (1.18)

Table 7 Coefficients for diagnosis, cognition, and racial differences and connectivity between the left and right anterior putamen and other regions of interest.

Left Anterior Putamen									
	Diagnosis			Cognition			Lower in AA with NC		
	B	t	p	B	t	p	B	t	p
Precentral Gyrus	-0.07	-0.81	0.42	**0.13**	**1.65**	**0.05**	**0.13**	**2.28**	**0.02**
Postcentral Gyrus	-0.07	-0.78	0.43	**0.14**	**1.79**	**0.05**	0.06	1.05	**0.29**
Superior Frontal Gyrus	-0.05	-0.25	0.8	-0.03	-1.43	0.15	**0.1**	**2.09**	**0.03**
Middle Frontal Gyrus	-0.12	-0.56	0.58	-0.01	-0.58	0.56	**0.14**	**2.81**	**0.01**
Posterior Putamen	0.12	0.56	0.57	0	0.03	0.98	0.04	0.8	0.43
Caudate	0.18	0.09	0.93	0	0.05	0.96	0.02	0.04	0.66
Insula	0.07	0.34	0.73	-0.02	-1.01	0.31	0.08	1.52	0.13

Right Anterior Putamen									
	Diagnosis			Cognition			Lower in AA with NC		
	B	t	p	B	t	p	B	t	p
Precentral Gyrus	**0.13**	**1.65**	**0.05**	**0.04**	**1.7**	**0.04**	0.07	1.23	0.22
Postcentral Gyrus	**0.14**	**1.79**	**0.05**	**0.05**	**2.21**	**0.03**	0.06	1.09	0.28
Superior Frontal Gyrus	-0.07	-0.31	0.76	-0.02	-1.39	0.16	**0.12**	**2.27**	**0.02**
Middle Frontal Gyrus	-0.12	-0.64	0.52	-0.02	-1.02	0.31	**0.13**	**2.3**	**0.02**
Posterior Putamen	0.11	0.47	0.64	-0.01	-0.66	0.51	-0.01	-0.11	0.91
Caudate	-0.21	-0.93	0.35	0	-0.36	0.72	0.05	0.96	0.34
Insula	0.1	0.45	.66	-0.02	-1.22	0.22	0.04	0.91	0.36

5 CONCLUSION

In the following sections we integrate our findings across aims. We first introduce our research questions and a summary of related findings. We then discuss findings that are not dependent on race within the DMN and the putamen and integrate these findings across networks. This is followed by a discussion of race dependent findings in both the DMN and cortical output putamen nodes, and how these biomarker to connectivity relationships inform our understanding of AD within AAs. We then review the role, or lack thereof, of WMH in explaining these relationships, and review other potential explanations for our findings. We conclude with a discussion of race and how this study answers, but also poses a variety of questions related to how we should operationalize race in future research.

5.1 Research Questions

The following section includes our research questions as well as a summary of the findings for each question.

Do African Americans have different connectivity to AD biomarker relationships than NHWs within the DMN and its subnetworks?

African Americans exhibit a connectivity profile different from that of NHWs. Contrary to NHW models, precuneus and posterior cingulate connectivity to regions of the dorsomedial subsystem increases as disease burden increases.

Does putaminal connectivity relate to AD biomarkers?

Connectivity between cortical inputs and the anterior putamen correlates with Alzheimer's disease burden such that as CSF Aβ42 decreased, connectivity between the anterior putamen and pre and post central gyri increased. In the right hemisphere, as cognitive performance decreased, connectivity increased in these same regions.

Does race modify these relationships between putaminal connectivity and AD biomarkers?

In the data from the African American participants, as CSF Aβ42 decreased, connectivity between the anterior putamen and the superior and middle frontal gyri also decreased.

Do hyperintensities in the DMN and in the putamen networks explain the observed racial differences?

In our sample, hyperintensities in the DMN did not explain the significant race X Aβ42 interaction for DMN connectivity, and did not account for the racial group differences in connectivity that we observed between APu and superior and middle frontal connectivity. However, regional hyperintensities within the putamen and these cortical output regions was related to connectivity in the left hemisphere in African Americans, such that as regional WMH burden increased, connectivity also decreased.

5.2 Integrating race independent connectivity associations with AD biomarkers

We identified a number of regions for which the relationships between connectivity and AD biomarkers were consistent across racial groups. In the DMN, these measures include connectivity between regions of the medial temporal lobe subsystem and between the midline core and medial temporal subsystems such that as CSF t-Tau increased, connectivity also increased. Within the putamen network, the consistent measures include connectivity between the anterior putamen and the pre and post central gyri. Within these regions, as disease burden (measured by the particular biomarker) increased, connectivity also increased. Typically individuals with a higher AD burden exhibit lower connectivity between DMN regions, but results are inconsistent in the putamen[64,258]. The increased connectivity that we observed within the DMN may be driven by the relatively larger group of individuals with MCI compared to AD. Because an increase in connectivity is often observed in MCI[59], and many studies consider diagnostic categories instead of continuous biomarker measures, and only a few studies have examined DMN subnetworks in AD[259,260], our results may not directly map onto previous studies. However, because the DMN subnetworks have unique functions measures (i.e. MTL correlates with memory and midline core is responsible for self-reflection)[62], and do not exhibit uniform relationships

with biomarkers as observed in the first aim, we recommend utilizing these subnetworks in future studies investigating DMN connectivity and continuous relationships with biomarkers.

Connectivity between the anterior putamen and its cortical input nodes (pre-post central gyrus) were related to both cognition and amyloid. The hyperconnectivity that we observed could be a pathological response to disease presence, or functional compensation as other regions begin to succumb the effect of AD. These particular measures of connectivity were independent of race, and thus we would recommend them as ROI's in future studies in diverse cohort. If others achieve replication of our results within this network, we could then recommend that this network be a preferred network of study in samples with diverse of individuals across the disease spectrum of AD. A previous EEG study identified hyperexcitability in the presence of AD within the sensorimotor cortex[261], despite the fact that this region is relatively spared from atrophy. This finding highlights an advantage of functional connectivity approaches, as it can examine complex neurological interactions beyond cell death. A summary figure of the race independent relationships is included below.
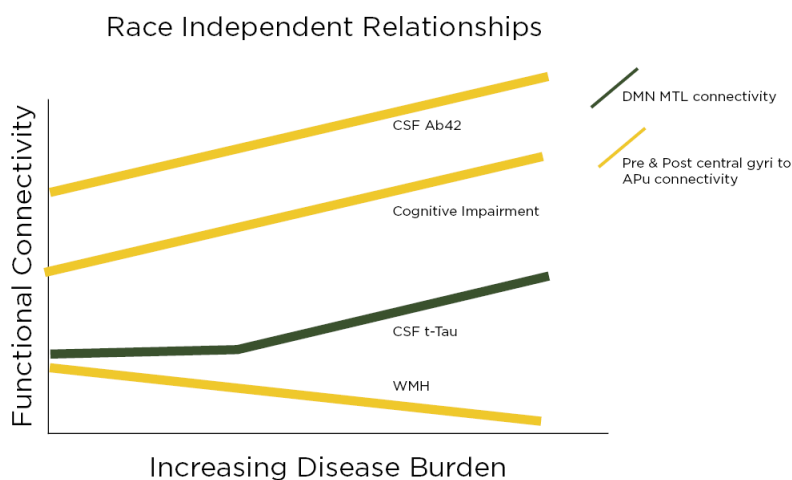
Figure 111 Summary figure of general race independent relationships between increasing disease burden as measured by AD biomarkers. Green line indicates the DMN MTL functional connectivity. Yellow indicates pre and post central gyri connectivity. DMN MTL = Default mode network medial temporal lobe, APu = anterior putamen.

This works gives partial support to the amyloid hypothesis in that it is initial amyloid deposition that starts the dementia cascade. The DMN, the first network to be affected in the course of AD was

related to both CSF tau and amyloid[58]. However, the putamen and its cortical nodes were not related to tau, but more consistently related to amyloid. According to Braak staging, the frontal lobe is affected later in the course of disease[199]. The amyloid hypothesis states that amyloid build up causes a metabolic cascade that eventually leads to tau deposition, but precedes NFT's by many years[24]. Atrophy typically correlates more strongly with tau, as the NFTs are what may trigger cell death. Amyloid buildup may signal the first stages of AD, and generate some of the functional changes that can be observed in fMRI studies. The consistent amyloid relationships that we identified in the putamen analyses could also reflect the overall impact of amyloid even in normal aging, as amyloid plaques are fairly common even in individuals with intact cognition. Further research would benefit from amyloid PET[262] studies that identify whether regional amyloid buildup in the putamen network we describe relates to connectivity.

The fact that tau was related to DMN MTL connectivity, but not to fronto-putaminal connectivity is in line with previous literature[168]. We would likely see significant relationships between tau and connectivity in a larger set of individuals in the later stages of dementia. Amyloid emerges earlier, and our cohort did have early MCI and individuals with NC. Based on Braak staging, frontal regions are not typically inundated with tau until later in the disease[199], and our cohort did have a larger proportion of controls. It is likely that some of these individuals had amyloid deposition, but had not, or will never cross the threshold into the Braak stages of tau deposition in the frontal areas. Further tau-pet[45] studies of individuals with MCI and AD should investigate these regions to determine if regional tau deposition may correlate with connectivity in the putamen nodes that we identified.

We identified relationships with cognition and connectivity in both of our networks of interest. Although related inversely to connectivity within NHWs for our DMN measures, it is important to recognize that connectivity measures were related to cognition in Cohort 3, which included individuals across the dementia spectrum, including AAs with AD, and related to a variety of connectivity within the DMN between the midline core and dorsomedial subsystems. Within the putamen network, cognition correlated with connectivity measures in the right hemisphere, between the right anterior putamen and the right pre and post central gyri. The lack of many significant relationships between cognition and

connectivity identified between the putamen and network regions could be a result of the fact that our sample for the putamen connectivity analyses included a larger group of individuals who were younger and had normal cognition. Our findings could indicate that amyloid exerts greater influence on connectivity without much relationship to cognition in this putamen network particularly earlier in the stages of AD or eventual AD[153]. Before cognitive symptoms emerge, amyloid could exert influence on connectivity, in a variety of regions including the putamen and its cortical nodes, but connectivity in these regions may not exhibit relationships with cognition and tau until much later in the disease[263]. An alternative explanation could be that the cognitive tests utilized in these cohorts are better at detecting memory impairment than impairment in other cognitive domains. The cognitive scores utilized in the first aim were taken from an extensive cognitive battery, but the other cohorts only had the MMSE and the MoCA. While the MoCA is more sensitive to cognitive domains for which the putamen and the cortical nodes are responsible (motor and visual spatial impairment)[52], utilizing a different cognitive measure for each cohort likely introduces noise that obfuscates relationships between cognition and putamen connectivity, especially given the cultural bias associated with these assessments that often over-predicts cognitive impairment in African Americans[264]. Future studies will investigate individuals with MCI and AD to determine whether putamen connectivity does indeed exhibit relationships with tau and cognition and whether these alterations manifest in cognitive performance, and investigate the relationships between cognitive domains outside of memory and the relationship to putamen connectivity.

5.3 Race Dependent relationships with AD biomarkers

Current consensus drawn from functional, structural, and pathological studies is that the hippocampus and the DMN are the primary regions affected by Alzheimer's Disease[59]. While research of these areas has yielded a wealth of scientific findings with clinical utility, there are many questions about the etiology and disparities within AD that may be answered by broadening the scope beyond the DMN and hippocampus. The DMN has been thoroughly explored in AD, and results across studies with similar definitions of the DMN, and similar methodological approaches have fairly consistent findings indicating

that DMN within network connectivity is lower in individuals with AD compared to NC, and declines as the disease progresses[59]. This work adds to the current body of literature by replicating previous studies and that use the DMN subnetwork connectivity measures in our sample of NHWs, and providing measures that may be sensitive to the biological changes generated by diverse ethno-cultural backgrounds.

Our findings within the NHW sample support previous literature that, within this group, DMN connectivity typically declines as AD burden increases. Our data-driven ICA approach to identifying components of the DMN, rather than utilizing seed-maps, could have been responsible for the increases we observed in AA, in that our data driven component maps perhaps did not represent the established DMN regions. However, because we identified the typical pattern of AD-related connectivity decline in NHWs, we can be fairly certain our methodology choice does not account for the disparate connectivity to biomarker relationships that we observed.

African Americans are less likely to exhibit amnestic profiles than their NHW counterparts; they have slower cognitive and functional decline, and different predictors of cognition. These facts compounded with evidence for a unique functional profile point to a possible sub classification of Alzheimer's disease that includes a consideration of lifestyle and genetic risk factors. Some papers suggest that MCI is characterized by a temporary increase in DMN connectivity, followed by the gradual decline associated with AD. AAs in our sample could be exhibiting an extended MCI-like connectivity profile. The diagnosis of AD within AA could be generated by a lower level of pathology, yet is exacerbated by comorbidities such as vascular disease. This may seem counter intuitive, but it suggests contributing comorbidities extant in AAs cause AD symptoms to emerge with a much lower pathology burden than in NHWs. This also may contribute to their greater life expectancy as the AA phenotype of AD may not be as severe, and may be more attributable to other neurological burdens. These results would be in line with other studies that have identified slower rates of cognitive decline in African Americans[109], and these connectivity increases could be an extension of this MCI hyperconnected phase.

Further studies investigating a greater number of AA individuals with AD would be necessary to explore this hypothesis.

In Alzheimer's disease, the hippocampus is typically included in default mode network analyses[155]. The DMN supports self-referential cognitive processes, including memory. Lower functional connectivity between DMN regions typically correlates with worse general cognition, higher AD burden, and worse memory performance[63]. Our findings from the first aim provide a neurological basis for the increased prevalence of non-amnestic MCI in African Americans and possibly explain why cognitive decline tends to progress more slowly in African Americans. Cognitive assessments tend to rely heavily on working memory[265]. The MMSE and MoCA both include at last one question that relies on memory, and lower working memory capabilities can impair assessment performance even on questions designed to assess visuospatial abilities. MoCA is more sensitive to detecting cognitive impairment other than memory, but both of these assessments are most commonly used to detect Alzheimer's disease[265]. Cognitive tasks that specifically assess motor function may be more sensitive to AD detection in African Americans as a result of underlying vulnerable region.

African Americans exhibited decreased connectivity between the APu and superior and middle frontal gyrus as CSF $A\beta42$ decreased. It is possible that the hyperconnectivity between the cortical input regions and the APu that we observed is a form of functional compensation for connectivity decline in other brain regions. We observed a decline in connectivity between DMN nodes in NHWs as AD burden increases, and between APu and superior and middle frontal in AAs (Figure 11). In individuals with normal cognition, African Americans exhibited lower connectivity between the anterior putamen and the superior and middle frontal gyrus. This finding, coupled with the increase in connectivity between the putamen and the pre and post central gyrus across races suggests that while there are uniform relationships between AD pathology and motor-putamen circuits, downstream frontal regions may be preferentially affected by race.
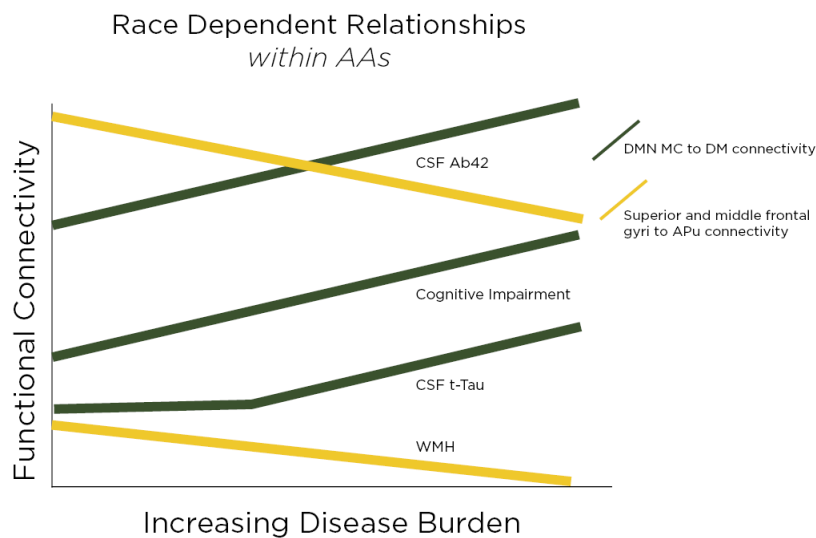
Race Dependent Relationships
within AAs

Figure 122 summary figure of race dependent relationships between increasing disease burden as measured by AD biomarkers. Only relationships within African Americans are displayed in this figure. Green line indicates the DMN MTL functional connectivity. Yellow indicates pre and post central gyri connectivity. DMN MTL = Default mode network medial temporal lobe, APu = anterior putamen.

We were not able to identify any variables that fully accounted the differences in biomarkers across racial groups. Many of the variables typically entangled with race, such as socio-economic status, hypertension, and white matter hyperintensity volume did not account for the effect of race on the biomarker to connectivity relationships in the DMN or in the putamen. Explanations for our findings could be a result of a complex interplay of biological and sociological factors whose measurement was outside the scope of this study. African Americans in these samples on average had lower socioeconomic status as measured by the ADI. However, including ADI in our analyses did not account for the significance of interaction terms. It is possible the ADI serves as a crude measure of SES, as it is merely a snapshot of where an individual resides at a particular time, and that is not the only factor entangled with race that may explain these racial differences. Low socio-economic-status[266] and perceived racial discrimination, both commonly reported in AAs[205], can affect the brain throughout the developmental spectrum. These factors create decreased connectivity across large scale brain networks that could create reliance on small scale networks[267], and these connections would then be reinforced over time. This could create a functional connectome that relies heavily on a functionally segregated, rather than integrated,

networks. Resilience to negative outcomes associated with challenging life events is associated with increased connectivity between the sensorimotor cortex and the putamen, a phenomenon that we observed in both races, though unrelated to resilience[268]. The slow decline observed in African Americans could be a result of the fact that previous reliance on small scale networks would be less impacted by Alzheimer's disease than NHWs, and that our NHW cohort exhibits functional integration that declines in response to disease. This could explain the slow decline exhibited by African Americans, as the networks would already be organized into functionally segregated networks, and the presence of disease may just enhance this underlying network structure. However, in NHWs in our sample, cognitive function would be primarily reliant on functional integration, and a disruption in this integration caused by AD pathology would lead to segregation and force networks to reorganize at a more rapid pace. A graph theoretical approach, particularly of longitudinal data, would allow us to test these hypotheses.

5.4 WMH and DMN connectivity

Our hypothesis that regional WMH within the DMN explained the significant effect of race on connectivity and biomarker relationships was not supported. WMH within these regions were not related to connectivity, and did not account for the significant race interaction term. However, this finding is not conclusive, and warrants further exploration in a larger dataset. Our cohort that included the connectivity and WMH data was not the same cohort used for our Aim 1 analyses. There were less participants in the WMH dataset, and we did not identify identical relationships between biomarkers and connectivity within this dataset. This is likely that we were underpowered to detect an effect, and that our cohorts had a different diagnostic distribution. In our WMH analysis dataset, we did not have any AAs with AD, only NC and MCI, but we did have NHWs across all diagnostic categories. Furthermore, the cognitive data from this cohort was limited to one general measure of cognition rather than from a battery of neuropsychological tests.

We did not identify regional differences between AA and NHW in WMH volume within the tracts of the DMN regions that we investigated. These DMN subsystem WMH volumes were not related

to CSF Aβ42 or CSF T-tau, even when we only utilized data from individuals with MCI and AD. If we did identify a significant relationship between CSF biomarkers and regional WMH volume, it would support the notion that WMH in these regions may be caused by AD pathology. However, our results do not support this hypothesis. Our findings are not conclusive, as we had a relatively small sample size (23 individuals with some form of cognitive impairment), and of those individuals, only 10 had corresponding CSF data. It is likely that we were underpowered, and a larger sample size would be necessary to detect a significant relationship between WMH and CSF biomarkers, especially given the differences in CSF T-tau levels between NHW and AAs.

WMH within the default mode subnetworks did not mediate the race by biomarker interaction terms. This finding should not be taken as conclusive evidence that WMH do not play a role in DMN connectivity. We were not able to replicate same race and biomarker interactions that we identified in the cohort of our first aim. This is likely a result of the limited distribution of our sample across race and diagnostic categories. However, previous studies do support these findings. Studies have inconsistently identified a relationship between amyloid and WMH, and between tau and WMH[99,102,269]. Many of the studies that correlate tau with WMH do so at a pathological post-mortem level, and identify WMH based on pathology rather than MR imaging. Little research exists that probes the mechanistic relationship between tau and WMH, and without longitudinal models, it will be difficult to establish a causal relationship. However, as tau-pet becomes more widely used, answering this question will become more feasible.

5.5 WMH and Putamen Connectivity

This work illustrates the importance of considering not only racial groups in analyses of individuals with AD, but comorbidities. Ruling out individuals who have contributing comorbidities may be appropriate to generate models that specifically study mechanisms related only to AD, but if other comorbidities are in fact risk factors for the disease being studies[270], the synergistic mechanisms between the disease of study and the comorbidities will be largely ignored. This research emphasizes the important

role of the contributing factors of vascular insult in the form of small vessel disease, as represented by the presence of WMH in the brain. Because we identified WMH burden in many controls in the absence of elevated amyloid beta, WMH may be generated ahead of amyloid burden, and not directly caused by ad pathology. This WMH does play a role in decreasing basal ganglia function particularly in AAs, which manifests as lower mid and superior connectivity. It is likely that in fronto-putamen regions, WMH increases susceptibility to the effects of Aβ42, rather than Aβ42 generating WMH. This finding adds to the hypothesis that AD related WMH are located in more posterior and temporal regions[101] rather than frontal and subcortical WMH, which seem to be more vascular in nature[271]. This work also adds to the hypotheses that WMH can disrupt pathways not only along tracts, but also within nodes[65]. Current research is limited to tract specific findings, but this work demonstrates that nodal WMH can also influence functional connectivity, particularly in metabolically active areas sensitive to oxygen and nutrient deficits.

The putamen and thalamus are regions particularly vulnerable to ischemic changes[272]. Metabolic studies indicate that these regions are highly metabolically active. This increased metabolic activity would make them particularly susceptible to the oxygen and nutrient deficits generated by ischemia and small vessel disease[273]. However, it is not likely that putamen WMH are the cause of the connectivity relationships we identified as being related to AD. In this work, we identified what regions exhibit connectivity changes related to AD, and those related to WMH. These two factors likely have a synergistic effect on connectivity, with African Americans exhibiting greater susceptibility to WMH. Why AAs exhibit this vulnerability remains unclear.

The current work supports the notion that amyloid burden is not related to WMH etiology. Within the amyloid literature, the relationship between WMH and amyloid is also controversial. The evidence that amyloid and WMH have a causal relationship is weak, and many studies have found no relationship between the two biomarkers even across different modalities of amyloid measurement (amyloid pet, amyloid staining, and CSF amyloid).

5.6 Limitations & Future Directions

Our findings should be considered in context of this work's limitations. We did not have uniform measures across all participants. Our cognitive measures were different across the three cohorts, and we did not have regional WMH for all participants. We were able to identify consistent relationships between connectivity and cognition across the cohort despite this limitation, but the extensive cognitive battery with standardized scores as we have for cohort 2 would obviously provide more accurate measures of cognition that would not exhibit the racial bias evident in more general tests of cognition. The lack of AA individuals with AD in the WMH limits the generalizability and validity of our findings such that we cannot fully overlay our functional relationships identified in Aim 1 on our WMH results. Future analyses will explore regional WMH and connectivity in a larger cohort with particular emphasis on a larger number of AA individuals with AD.

Our analyses were limited to studying race and biomarker interaction terms, and considering the effects of gender were outside the scope of this study. In addition to race, gender also has biological and social definitions. Disparities exist between genders such that women are more likely to develop AD[274], but live longer than men with AD. Studying the impact of intersectionality in Alzheimer's Disease can widen the net of individuals with whom clinicians should consider at risk for AD and allow for more targeted public health campaigns and interventions to address some of the modifiable factors of AD that may be entangled with these social and biological categories.

Although we were able to include a large percentage of AA individuals across our cohorts, we did not have a sufficient number of AA individuals with AD to completely replicate our findings from Aim 1. While we did identify some consistent relationships across cohorts in cohort 1, a larger sample of AA individuals with AD would be ideal to determine the generalizability of our results. While this work does establish biological manifestations of health disparities, there are a number of biological and sociological factors that we did not consider that may play a role in the manifestation of these disparities. As previously mentioned, the sociological aspects of race, while socially constructed in nature, can generate disparate health outcomes. For example, perceived racial discrimination[205], lower socio-economic

status[275], education quality[276], and residential environment during childhood[252], family and community bonds, and resilience[277], all of which show differences across racial groups, can have negative and protective effects on brain health. Our sample of African Americans should in no way be taken as representative of all African Americans. A nuanced approach of examining the aforementioned variables should be the focus of future analyses, rather than broad categorization of individuals based on race. However, in order to increase participation of individuals of diverse in science studies and make the case for national investment of funds in this effort, establishing gross racial differences is the first step.

The only measures of pathology that we used were derived from CSF. While this is useful in determining the validity of our connectivity measures and whether they are related to gross levels of CSF tau and amyloid, it would be valuable to investigate the regional distribution of tau and amyloid through PET scans, and whether regional distribution of these pathologies are related to connectivity and regional WMH. This would enable us to more accurately add to the WMH etiology debate, and determine how these pathologies may affect connectivity, i.e. are tau and $A\beta 42$ within the DMN generating functional connectivity changes, or is the DMN responding to amyloid and tau deposition elsewhere is the brain.

This study used cross-sectional data across the disease spectrum to understand how biomarkers and connectivity are related to one another at varying levels of disease burden. However, to uncover casual mechanisms and develop disease trajectories that may be specific to a particular race, longitudinal models would be necessary. We modeled the biomarker and connectivity relationships using linear functions, as that is the simplest and most logical place to begin an analysis. However, our understanding of how CSF biomarkers change over the course of the disease is limited, particularly within African Americans. The relationship between CSF $A\beta 42$ and connectivity could be stronger in the earlier phases of the disease, and then plateau as the amyloid threshold for the development of AD is reached[37]. While this can be modeled in a cross sectional analysis, a longitudinal analysis would provide more sensitivity to track changes across disease development, and we can adjust current disease trajectory models to include race, and introduce regional staging of functional connectivity changes. We would also like to confirm that WMH emerge before functional connectivity changes using a longitudinal model, and whether CSF

tau and amyloid alterations in the CSF occur before the emergence of WMH. While it seems logical that WMH could influence FC, we are still not sure whether the two variables are correlated or causally related. It also seems logical that WMH would be present before CSF and tau alterations, but that is under the assumption that WMH are not caused by AD pathology[278]. While this study suggests that WMH are independent of AD pathology, a longitudinal analysis would provide more conclusive evidence either way.

This work brings into question the definition of race. Many people try to define race as a purely genetic concept[193], but the lines between races from a purely genetic standpoint are nonexistent in the US at least. In fact, many NHWs in the U.S. exhibit similar genetic profiles to AAs[279]. This leads others to argue that race is purely a social construct with little biological utility[11]. The answer most likely lies somewhere in the middle, as this work can attest to. A failing of this work is that we have had to include African Americans as one group, when in fact "African Americans" are a diverse minority group with a variety of socioeconomic, genetic, and lifestyle backgrounds. The term "African American" obviously has some utility in the clinic, as African Americans do have higher prevalence rates of AD[1]. However, when we controlled for many of the factors that could potentially explain the racial disparities that we identified, such as presence of vascular disease, type-2 diabetes, socio-economic status, and risk genes, we still had significant racial differences that no variable fully explained. This work supports the notion that "race" in the context of Alzheimer's Disease is more of a complex interplay between ethnicity, ancestry, and lifestyles, and that "ethno-cultural" group may more accurately describe the African American diaspora[280]. Furthermore, cohort effects may impact our results, as many of the older individuals in our studies grew up in a time of racial turmoil during or just after the conclusion of the civil rights movement[276]. While the current time leaves much to be desired in the area of race relations, the level of institutional racism present during the time of segregation and just after could create a lingering impression on brain health that cannot be captured by merely examining biological and lifestyle factors[276]. While we have to establish meaningful differences in order to encourage the inclusion of a diverse cohort

in future studies, we hope that in the future, more nuanced and precision approaches to quantifying ethno-cultural backgrounds can be adopted.

As this work conclusively shows, characterizing the functional profile of individuals with Alzheimer's disease must be an inclusive process. A one-brain-fits-all approach doesn't address the unique differences between sample populations. Even structural templates vary based on sample population, let alone functional connectomes with a larger number of variables. While we identified regions that did exhibit the same biomarker to connectivity patterns across races a number of these measures, particularly in the network most commonly studied in AD, we must carefully choose our regions of interest, and consider the makeup of our sample accordingly. Putamen input nodes seem to be consistently related to amyloid across races, while DMN connectivity should be considered with race as a variable of interest for analyses in cohorts that include African Americans and NHWs. If functional data is to be used as a biomarker for early detection of AD, or to predict conversion from MCI to AD, we must strive to create a profile that includes not just individuals from all backgrounds, but individuals who at the greatest risk of developing the disease.

.

REFERENCES

1. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement.* **6**, 158–194 (2010).

2. Morris, J. C. *et al.* Assessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer Disease. *JAMA Neurol.* **76**, 264–273 (2019).

3. Ighodaro, E. T. *et al.* Challenges and Considerations Related to Studying Dementia in Blacks/African Americans. *J. Alzheimers Dis. JAD* **60**, 1–10 (2017).

4. Balachandar, R. *et al.* A study of structural and functional connectivity in early Alzheimer's disease using rest fMRI and diffusion tensor imaging. *Int. J. Geriatr. Psychiatry* **30**, 497–504 (2015).

5. Jalilianhasanpour, R., Beheshtian, E., Sherbaf, G., Sahraian, S. & Sair, H. I. Functional Connectivity in Neurodegenerative Disorders: Alzheimer's Disease and Frontotemporal Dementia. *Top. Magn. Reson. Imaging* **28**, (2019).

6. Ossenkoppele, R. *et al.* Tau covariance patterns in Alzheimer's disease patients match intrinsic connectivity networks in the healthy brain. *NeuroImage Clin.* **23**, 101848 (2019).

7. Keller, A. S. & Christopher, L. Distinct Phases of Tau, Amyloid, and Functional Connectivity in Healthy Older Adults. *J. Neurosci. Off. J. Soc. Neurosci.* **37**, 8857–8859 (2017).

8. Chabran, E. *et al.* Changes in gray matter volume and functional connectivity in dementia with Lewy bodies compared to Alzheimer's disease and normal aging: implications for fluctuations. *Alzheimers Res. Ther.* **12**, 9 (2020).

9. Van Hooren, R. W. E., Riphagen, J. M., Jacobs, H. I. L. & For the Alzheimer's Disease Neuroimaging Initiative. Inter-network connectivity and amyloid-beta linked to cognitive decline in preclinical Alzheimer's disease: a longitudinal cohort study. *Alzheimers Res. Ther.* **10**, 88 (2018).

10. National Research Council. *Critical Perspectives on Racial and Ethnic Differences in Health in Late Life*. (The National Academies Press, 2004). doi:10.17226/11086.

11. Yudell, M., Roberts, D., DeSalle, R. & Tishkoff, S. Taking race out of human genetics. *Science* **351**, 564 (2016).

12. Barnes, L. L. & Bennett, D. A. Alzheimer's Disease In African Americans: Risk Factors And Challenges For The Future. *Health Aff. Proj. Hope* **33**, 580–586 (2014).

13. Weiner, M. F. Perspective on Race and Ethnicity in Alzheimer's Disease Research. *Alzheimers Dement. J. Alzheimers Assoc.* **4**, 233–238 (2008).

14. KOCA, E., TAŞKAPILIOĞLU, Ö. & BAKAR, M. Caregiver Burden in Different Stages of Alzheimer's Disease. *Arch. Neuropsychiatry* **54**, 82–86 (2017).

15. Howell, J. C. *et al.* Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. *Alzheimers Res. Ther.* **9**, 88 (2017).

16. Kim, C. X. *et al.* Sex and ethnic differences in 47 candidate proteomic markers of cardiovascular disease: the Mayo Clinic proteomic markers of arteriosclerosis study. *PloS One* **5**, e9065–e9065 (2010).

17. Hollingworth, P. *et al.* Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* **43**, (2011).

18. Weuve, J. *et al.* Cognitive Aging in Black and White Americans: Cognition, Cognitive Decline, and Incidence of Alzheimer Disease Dementia. *Epidemiology* **29**, (2018).

19. Zhou, Y. *et al.* African Americans are less likely to enroll in preclinical Alzheimer's disease clinical trials. *Alzheimers Dement. N. Y. N* **3**, 57–64 (2016).

20. Brodaty, H. *et al.* Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. *Ann. Epidemiol.* **24**, 63–71 (2014).

21. Williams, M. M. *et al.* Barriers and Facilitators of African American Participation in Alzheimer's Disease Biomarker Research. *Alzheimer Dis. Assoc. Disord.* **24**, S24–S29 (2010).

22. Jefferson, A. L. *et al.* Factors Associated With African-American and White Elders' Participation in a Brain Donation Program. *Alzheimer Dis. Assoc. Disord.* **25**, 11–16 (2011).

23. Wendler, D. *et al.* Are racial and ethnic minorities less willing to participate in health research? *PLoS Med.* **3**, e19–e19 (2006).

24. Goedert, M. & Spillantini, M. G. A Century of Alzheimer's Disease. *Science* **314**, 777 (2006).

25. Wade, J. P. H. *et al.* The Clinical Diagnosis of Alzheimer's Disease. *Arch. Neurol.* **44**, 24–29 (1987).

26. Adi Kurnia Susanto, T., Pua, E. & Zhou, J. *Cognition, Brain Atrophy, and Cerebrospinal Fluid Biomarkers Changes from Preclinical to Dementia Stage of Alzheimer's Disease and the Influence of Apolipoprotein E.* vol. 45 (2014).

27. Beach, T. G., Monsell, S. E., Phillips, L. E. & Kukull, W. Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J. Neuropathol. Exp. Neurol.* **71**, 266–273 (2012).

28. Albert, M. S. *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association Workgroup. *Alzheimers Dement* **7**, (2011).

29. Bateman, R. J., Wen, G., Morris, J. C. & Holtzman, D. M. Fluctuations of CSF amyloid-β levels: implications for a diagnostic and therapeutic biomarker. *Neurology* **68**, (2007).

30. De Leon, M. J. *et al.* MRI and CSF studies in the early diagnosis of Alzheimer's disease. *J. Intern. Med.* **256**, 205–223 (2004).

31. Han, S. D. *et al.* Beta Amyloid, Tau, Neuroimaging, and Cognition: Sequence Modeling of Biomarkers for Alzheimer's Disease. *Brain Imaging Behav.* **6**, 610–620 (2012).

32. Kametani, F. & Hasegawa, M. Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. *Front. Neurosci.* **12**, 25 (2018).

33. Reitz, C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. *Int. J. Alzheimers Dis.* **2012**, 369808–369808 (2012).

34. Hu, W. T. *et al.* CSF β-amyloid 1–42 – what are we measuring in Alzheimer's disease? *Ann Clin Transl Neurol* **2**, (2015).

35. Wang, Y. & Mandelkow, E. Tau in physiology and pathology. *Nat Rev Neurosci* **17**, 22–35 (2016).

36. Brier, M. R. *et al.* Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. *Sci. Transl. Med.* **8**, 338ra66-338ra66 (2016).

37. Iqbal, K., Liu, F., Gong, C.-X. & Grundke-Iqbal, I. Tau in Alzheimer Disease and Related Tauopathies. *Curr. Alzheimer Res.* **7**, 656–664 (2010).

38. Bejanin, A. *et al.* Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* **140**, 3286–3300 (2017).

39. Petersen, R. C. *et al.* Aging, Memory, and Mild Cognitive Impairment. *Int. Psychogeriatr.* **9**, 65–69 (1997).

40. Jahn, H. Memory loss in Alzheimer's disease. *Dialogues Clin. Neurosci.* **15**, 445–454 (2013).

41. Csukly, G. *et al.* The Differentiation of Amnestic Type MCI from the Non-Amnestic Types by Structural MRI. *Front. Aging Neurosci.* **8**, 52 (2016).

42. Mez, J. *et al.* Dysexecutive versus amnestic Alzheimer's disease subgroups: Analysis of demographic, genetic, and vascular factors. *Alzheimer Dis. Assoc. Disord.* **27**, 218–225 (2013).

43. Baudic, S. *et al.* Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Arch. Clin. Neuropsychol.* **21**, 15–21 (2006).

44. Vemuri, P. & Jack, C. R. Role of structural MRI in Alzheimer's disease. *Alzheimers Res. Ther.* **2**, 23 (2010).

45. Seemiller, J., Tahmasian, M., Yakushev, I. & Drzezga, A. In vivo Tau-PET indicates expansion of tau pathology within the default mode network in Alzheimer's disease. *Alzheimers Dement. J. Alzheimers Assoc.* **11**, P109–P110 (2015).

46. Berg, C. N., Sinha, N. & Gluck, M. A. The Effects of APOE and ABCA7 on Cognitive Function and Alzheimer's Disease Risk in African Americans: A Focused Mini Review. *Front. Hum. Neurosci.* **13**, 387 (2019).

47. Turney, I. C. *et al.* APOE ε4 and resting-state functional connectivity in racially/ethnically diverse older adults. *Alzheimers Dement. Diagn. Assess. Dis. Monit.* **12**, e12094 (2020).

48. Livney, M. G. *et al.* Ethnoracial differences in the clinical characteristics of Alzheimer's disease at initial presentation at an urban Alzheimer's disease center. *Am J Geriatr Psychiatry* **19**, (2011).

49. Gamaldo, A. A., Allaire, J. C., Sims, R. C. & Whitfield, K. E. Assessing Mild Cognitive Impairment among Older African Americans. *Int. J. Geriatr. Psychiatry* **25**, 748–755 (2010).

50. Campbell, A. L. *et al.* Caveats in the neuropsychological assessment of African Americans. *J. Natl. Med. Assoc.* **94**, 591–601 (2002).

51. Rossetti, H. C. *et al.* Montreal Cognitive Assessment Performance among Community-Dwelling African Americans. *Arch. Clin. Neuropsychol.* **32**, 238–244 (2017).

52. Romero, H. R. *et al.* Challenges in the Neuropsychological Assessment of Ethnic Minorities: Summit Proceedings. *Clin. Neuropsychol.* **23**, 761–779 (2009).

53. Manly, J. J. Advantages and Disadvantages of Separate Norms for African Americans. *Clin. Neuropsychol.* **19**, 270–275 (2005).

54. Norman, M. A. *et al.* Demographically Corrected Norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. *J. Clin. Exp. Neuropsychol.* **33**, 793–804 (2011).

55. Lucas, J. A. *et al.* Mayo's Older African Americans Normative Studies: norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, WRAT-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation. *Clin Neuropsychol* **19**, (2005).

56. Agosta, F. *et al.* Resting state fMRI in Alzheimer's disease: beyond the default mode network. *Neurobiol. Aging* **33**, 1564–1578 (2012).

57. Kim, J., Kim, Y.-H. & Lee, J.-H. Research Report: Hippocampus–precuneus functional connectivity as an early sign of Alzheimer's disease: A preliminary study using structural and functional magnetic resonance imaging data. *Brain Res.* **1495**, 18–29 (2013).

58. Zhou, J., Liu, S., Ng, K. K. & Wang, J. Applications of Resting-State Functional Connectivity to Neurodegenerative Disease. *Neuroimaging Clin. N. Am.* **27**, 663–683 (2017).

59. Anckaerts, C. *et al.* Early functional connectivity deficits and progressive microstructural alterations in the TgF344-AD rat model of Alzheimer's Disease: A longitudinal MRI study. *Neurobiol. Dis.* (2018).

60. Sheline, Y. I. & Raichle, M. E. Resting State Functional Connectivity in Preclinical Alzheimer's Disease: A Review. *Biol. Psychiatry* **74**, 340–347 (2013).

61. Badhwar, A. *et al.* Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimers Dement. Amst. Neth.* **8**, 73–85 (2017).

62. Bluhm, R. L. *et al.* Default mode network connectivity: effects of age, sex, and analytic approach. *NeuroReport* **19**, (2008).

63. Greicius, M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr. Opin. Neurol.* **21**, (2008).

64. Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R. & Buckner, R. L. Functional-Anatomic Fractionation of the Brain's Default Network. *Neuron* **65**, 550–562 (2010).

65. Greicius, M. D., Srivastava, G., Reiss, A. L. & Menon, V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 4637–4642 (2004).

66. Binnewijzend, M. A. A. *et al.* Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* **33**, 2018–2028 (2012).

67. Zhu, D. C., Majumdar, S., Korolev, I. O., Berger, K. L. & Bozoki, A. C. Alzheimer's Disease and Amnestic Mild Cognitive Impairment Weaken Connections Within the Default-Mode Network: A Multi-Modal Imaging Study. *J. Alzheimers Dis.* **34**, 969–984 (2013).

68. Hafkemeijer, A., van der Grond, J. & Rombouts, S. A. R. B. Imaging the default mode network in aging and dementia. *Imaging Brain Aging Neurodegener. Dis.* **1822**, 431–441 (2012).

69. Westlye, E. T., Lundervold, A., Rootwelt, H., Lundervold, A. J. & Westlye, L. T. Increased Hippocampal Default Mode Synchronization during Rest in Middle-Aged and Elderly APOE ε4 Carriers: Relationships with Memory Performance. *J. Neurosci.* **31**, 7775 (2011).

70. Harrison, T. M., Burggren, A. C., Small, G. W. & Bookheimer, S. Y. Altered memory-related functional connectivity of the anterior and posterior hippocampus in older adults at increased genetic risk for Alzheimer's disease. *Hum. Brain Mapp.* **37**, 366–380 (2016).

71. Toussaint, P.-J. *et al.* Characteristics of the default mode functional connectivity in normal ageing and Alzheimer's disease using resting state fMRI with a combined approach of entropy-based and graph theoretical measurements. *NeuroImage* **101**, 778–786 (2014).

72. Clark, U. S., Miller, E. R. & Hegde, R. R. Experiences of Discrimination Are Associated With Greater Resting Amygdala Activity and Functional Connectivity. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **3**, 367–378 (2018).

73. Crane, N. T., Hayes, J. M., Viviano, R. P., Bogg, T. & Damoiseaux, J. S. Resting-state functional brain connectivity in a predominantly African-American sample of older adults: exploring links among personality traits, cognitive performance, and the default mode network. *Personal. Neurosci.* **3**, e3–e3 (2020).

74. Fani, N. *et al.* Fear-potentiated startle during extinction is associated with white matter microstructure and functional connectivity. *Cortex J. Devoted Study Nerv. Syst. Behav.* **64**, 249–259 (2015).

75. Holmes, C. J. *et al.* Parenting and Salience Network Connectivity Among African Americans: A Protective Pathway for Health-Risk Behaviors. *Biol. Psychiatry* **84**, 365–371 (2018).

76. Fani, N. *et al.* STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN POSTTRAUMATIC STRESS DISORDER: ASSOCIATIONS WITH FKBP5. *Depress. Anxiety* **33**, 300–307 (2016).

77. de Jong, L. W. *et al.* Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain J. Neurol.* **131**, 3277–3285 (2008).

78. Sun, Y. *et al.* Characterizing Brain Iron Deposition in Patients with Subcortical Vascular Mild Cognitive Impairment Using Quantitative Susceptibility Mapping: A Potential Biomarker. *Front. Aging Neurosci.* **9**, 81–81 (2017).

79. Liu, C. *et al.* Characterizing brain iron deposition in subcortical ischemic vascular dementia using susceptibility-weighted imaging: An in vivo MR study. *Behav. Brain Res.* **288**, 33–38 (2015).

80. Hamasaki, H. *et al.* Tauopathy in basal ganglia involvement is exacerbated in a subset of patients with Alzheimer's disease: The Hisayama study. *Alzheimers Dement. Amst. Neth.* **11**, 415–423 (2019).

81. Youn, Y. C. *et al.* (11)C-PIB PET imaging reveals that amyloid deposition in cases with early-onset Alzheimer's disease in the absence of known mutations retains higher levels of PIB in the basal ganglia. *Clin. Interv. Aging* **12**, 1041–1048 (2017).

82. Kotz, S. A., Schwartze, M. & Schmidt-Kassow, M. Non-motor basal ganglia functions: a review and proposal for a model of sensory predictability in auditory language perception. *Cortex J. Devoted Study Nerv. Syst. Behav.* **45**, 982–90 (2009).

83. Leh, S. E., Petrides, M. & Strafella, A. P. The neural circuitry of executive functions in healthy subjects and Parkinson's disease. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **35**, 70–85 (2010).

84. Manes, J. L. *et al.* Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease. *Brain Behav.* **8**, e01073 (2018).

85. Szewczyk-Krolikowski, K. *et al.* Functional connectivity in the basal ganglia network differentiates PD patients from controls. *Neurology* **83**, 208–214 (2014).

86. Cacciola, A. *et al.* A Connectomic Analysis of the Human Basal Ganglia Network. *Front. Neuroanat.* **11**, 85–85 (2017).

87. Wymbs, N. F., Bassett, D. S., Mucha, P. J., Porter, M. A. & Grafton, S. T. Differential recruitment of the sensorimotor putamen and frontoparietal cortex during motor chunking in humans. *Neuron* **74**, 936–946 (2012).

88. de Jong, L. W. *et al.* Shape Abnormalities of the Striatum in Alzheimer's Disease. *J. Alzheimers Dis.* **23**, 49–59 (2011).

89. Zhang, H. *et al.* Gray matter atrophy patterns of mild cognitive impairment subtypes. *J. Neurol. Sci.* **315**, 26–32 (2012).

90. Tabatabaei-Jafari, H., Walsh, E., Shaw, M. E., Cherbuin, N. & Alzheimer's Disease Neuroimaging Initiative (ADNI). The cerebellum shrinks faster than normal ageing in Alzheimer's disease but not in mild cognitive impairment. *Hum. Brain Mapp.* **38**, 3141–3150 (2017).

91. Lin, C.-Y., Chen, C.-H., Tom, S. E., Kuo, S.-H. & for the Alzheimer's Disease Neuroimaging Initiative. Cerebellar Volume Is Associated with Cognitive Decline in Mild Cognitive Impairment: Results from ADNI. *The Cerebellum* **19**, 217–225 (2020).

92. Debette, S. & Markus, H. S. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* **341**, c3666–c3666 (2010).

93. Wardlaw, J. M., Valdés Hernández, M. C. & Muñoz-Maniega, S. What are White Matter Hyperintensities Made of?: Relevance to Vascular Cognitive Impairment. *J. Am. Heart Assoc. Cardiovasc. Cerebrovasc. Dis.* **4**, e001140 (2015).

94. Yoshita, M. *et al.* Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. *Neurology* **67**, 2192–2198 (2006).

95. Morris, Z. *et al.* Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *The BMJ* **339**, b3016 (2009).

96. Debette, S. *et al.* Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke* **41**, 600–606 (2010).

97. Gons, R. A. R. *et al.* Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. *Brain* **134**, 2116–2124 (2011).

98. Tamura, Y. & Araki, A. Diabetes mellitus and white matter hyperintensity. *Geriatr. Gerontol. Int.* **15**, 34–42 (2015).

99. Brisset, M. *et al.* Large-vessel correlates of cerebral small-vessel disease. *Neurology* **80**, 662–669 (2013).

100. Brickman, A. M., Muraskin, J. & Zimmerman, M. E. Structural neuroimaging in Alzheimer's disease: do white matter hyperintensities matter? *Dialogues Clin. Neurosci.* **11**, 181–190 (2009).

101. Graff-Radford, J. *et al.* White matter hyperintensities: relationship to amyloid and tau burden. *Brain* **142**, 2483–2491 (2019).

102. Prins, N. D. & Scheltens, P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat. Rev. Neurol.* **11**, 157–165 (2015).

103. Provenzano, F. A. *et al.* White matter hyperintensities and cerebral amyloidosis: necessary and sufficient for clinical expression of Alzheimer disease? *JAMA Neurol.* **70**, 455–461 (2013).

104. McAleese, K. E. *et al.* Parietal white matter lesions in Alzheimer's disease are associated with cortical neurodegenerative pathology, but not with small vessel disease. *Acta Neuropathol. (Berl.)* **134**, 459–473 (2017).

105. Yoshiura, T. *et al.* Diffusion tensor in posterior cingulate gyrus: correlation with cognitive decline in Alzheimer's disease. *NeuroReport* **13**, (2002).

106. Kim, J. H. *et al.* Regional white matter hyperintensities in normal aging, single domain amnestic mild cognitive impairment, and mild Alzheimer's disease. *J. Clin. Neurosci.* **18**, 1101–1106 (2011).

107. Provenzano, F. A. *et al.* White matter hyperintensities and cerebral amyloidosis: Necessary and sufficient for clinical expression of Alzheimer's disease? *JAMA Neurol.* **70**, 455–461 (2013).

108. Taylor, A. N. W. *et al.* Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease. *Alzheimers Dement. J. Alzheimers Assoc.* **13**, 225–235 (2017).

109. Langen, C. D. *et al.* White matter lesions relate to tract-specific reductions in functional connectivity. *Neurobiol. Aging* **51**, 97–103 (2017).

110. Reijmer, Y. D. *et al.* Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities. *NeuroImage* **117**, 222–229 (2015).

111. Gavett, B. E. *et al.* Ethnoracial differences in brain structure change and cognitive change. *Neuropsychology* **32**, 529–540 (2018).

112. DeCarli, C. *et al.* Brain Behavior Relationships amongst African Americans, Caucasians and Hispanics. *Alzheimer Dis. Assoc. Disord.* **22**, 382–391 (2008).

113.   Brickman AM, Schupf N, Manly JJ & et al. Brain morphology in older african americans, caribbean hispanics, and whites from northern manhattan. *Arch. Neurol.* **65**, 1053–1061 (2008).

114.   Meier, I. B. *et al.* White Matter Predictors of Cognitive Functioning in Older Adults. *J. Int. Neuropsychol. Soc.* **18**, 414–427 (2012).

115.   Barnes, L. L. *et al.* Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology* **85**, (2015).

116.   Brickman, A. M. *et al.* Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer's disease in the community. *Arch. Neurol.* **69**, 1621–1627 (2012).

117.   Hahn, C. *et al.* Apathy and white matter integrity in Alzheimer's disease: a whole brain analysis with tract-based spatial statistics. *PLoS One* **8**, e53493 (2013).

118.   Taylor, A. N. W. *et al.* Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease. *Alzheimers Dement.* **13**, 225–235 (2017).

119.   Brancati FL, Kao W, Folsom AR, Watson RL & Szklo M. Incident type 2 diabetes mellitus in african american and white adults: The atherosclerosis risk in communities study. *JAMA* **283**, 2253–2259 (2000).

120.   Saab, K. R. *et al.* New Insights on the Risk for Cardiovascular Disease in African Americans: The Role of Added Sugars. *J. Am. Soc. Nephrol.* **26**, 247 (2015).

121.   Ghidei, W. & Collins, T. C. African Americans and Peripheral Arterial Disease: A Review Article. *ISRN Vasc. Med.* **2012**, 1–9 (2012).

122.   Akter, K. *et al.* Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br. J. Clin. Pharmacol.* **71**, 365–376 (2011).

123.   Knopman, D. S. *et al.* Vascular risk factors and longitudinal changes on brain MRI. *Neurology* **76**, 1879 (2011).

124.   Gottesman RF, Schneider AC, Zhou Y & et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA* **317**, 1443–1450 (2017).

125. Stevens-Watkins, D., Perry, B., Pullen, E., Jewell, J. & Oser, C. *Examining the Associations of Racism, Sexism, and Stressful Life Events on Psychological Distress Among African-American Women*. vol. 20 (2014).

126. Turner, A. D., James, B. D., Capuano, A. W., Aggarwal, N. T. & Barnes, L. L. Perceived Stress and Cognitive Decline in Different Cognitive Domains in a Cohort of Older African Americans. *Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry* **25**, 25–34 (2017).

127. Al Hazzouri, A. Z., Elfassy, T., Sidney, S., Jacobs, D. R., Jr. & Yaffe, K. Impact of sustained economic hardship on cognitive functioning. *Alzheimers Dement. J. Alzheimers Assoc.* **11**, P591 (2015).

128. Kalaria, R. N. *et al.* Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol.* **7**, 812–826 (2008).

129. Shpanskaya, K. S. *et al.* Educational attainment and hippocampal atrophy in the Alzheimer's disease neuroimaging initiative cohort. *J. Neuroradiol.* **41**, 350–357 (2014).

130. Russ, T. C. *et al.* Socioeconomic status as a risk factor for dementia death: individual participant meta-analysis of 86 508 men and women from the UK. *Br. J. Psychiatry J. Ment. Sci.* **203**, 10–17 (2013).

131. Williams, D. R., Priest, N. & Anderson, N. B. Understanding associations among race, socioeconomic status, and health: Patterns and prospects. *Health Psychol. Off. J. Div. Health Psychol. Am. Psychol. Assoc.* **35**, 407–411 (2016).

132. Egede, L. E. Race, ethnicity, culture, and disparities in health care. *J. Gen. Intern. Med.* **21**, 667–669 (2006).

133. Tang, M. X. *et al.* Relative risk of Alzheimer disease and age-at-onset distributions, based on APOE genotypes among elderly African Americans, Caucasians, and Hispanics in New York City. *Am. J. Hum. Genet.* **58**, 574–584 (1996).

134. Logue, M. W. *et al.* A comprehensive genetic association study of Alzheimer disease in African Americans. *Arch Neurol* **68**, (2011).

135. Hendrie, H. C. *et al.* APOE ε4 and the risk for Alzheimer disease and cognitive decline in African Americans and Yoruba. *Int. Psychogeriatr. IPA* **26**, 977–985 (2014).

136. Reitz, C. *et al.* Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ε4, and the risk of late-onset Alzheimer disease in African Americans. *JAMA* **309**, (2013).

137. Britton, A. *et al.* Threats to Applicability of Randomised Trials: Exclusions and Selective Participation. *J. Health Serv. Res. Policy* **4**, 112–121 (1999).

138. Gill, P. S., Plumridge, G., Khunti, K. & Greenfield, S. Under-representation of minority ethnic groups in cardiovascular research: a semi-structured interview study. *Fam. Pract.* **30**, 233–241 (2013).

139. Shin, J. & Doraiswamy, P. M. Underrepresentation of African-Americans in Alzheimer's Trials: A Call for Affirmative Action. *Front. Aging Neurosci.* **8**, 123 (2016).

140. Fitzpatrick, A. L. *et al.* Incidence and Prevalence of Dementia in the Cardiovascular Health Study. *J. Am. Geriatr. Soc.* **52**, 195–204 (2004).

141. Potter, G. G. *et al.* Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and whites. *Alzheimers Dement. J. Alzheimers Assoc.* **5**, 445–453 (2009).

142. Wilson, R. S., Capuano, A. W., Sytsma, J., Bennett, D. A. & Barnes, L. L. Cognitive Aging in Older Black and White Persons. *Psychol. Aging* **30**, 279–285 (2015).

143. Logue, M. W. *et al.* Two rare AKAP9 variants are associated with Alzheimer disease in African Americans. *Alzheimers Dement. J. Alzheimers Assoc.* **10**, 609-618.e11 (2014).

144. Bonner, G. J., Darkwa, O. K. & Gorelick, P. B. Autopsy Recruitment Program for African Americans. *Alzheimer Dis. Assoc. Disord.* **14**, (2000).

145. Ozturk, T. *et al.* Linked CSF reduction of phosphorylated tau and IL-8 in HIV associated neurocognitive disorder. *Sci. Rep.* **9**, 8733 (2019).

146. Wharton, W. *et al.* Interleukin 9 alterations linked to alzheimer disease in african americans. *Ann. Neurol.* **0**, (2019).

147.   Beason-Held, L. L. *et al.* Changes in brain function occur years before the onset of cognitive impairment. *J. Neurosci. Off. J. Soc. Neurosci.* **33**, 18008–18014 (2013).

148.   Damoiseaux, J. S., Prater, K. E., Miller, B. L. & Greicius, M. D. Functional connectivity tracks clinical deterioration in Alzheimer's disease. *Neurobiol. Aging* **33**, 828.e19-828.e8.28E30 (2012).

149.   Brier, M. R. *et al.* Loss of Intranetwork and Internetwork Resting State Functional Connections with Alzheimer's Disease Progression. *J. Neurosci.* **32**, 8890 (2012).

150.   Damoiseaux, J. S. *et al.* Reduced resting-state brain activity in the "default network" in normal aging. *Cereb. Cortex* **18**, 1856–1864 (2008).

151.   He, X. *et al.* Abnormal salience network in normal aging and in amnestic mild cognitive impairment and Alzheimer's disease. *Hum. Brain Mapp.* **35**, 3446–3464 (2014).

152.   Simioni, A. C., Dagher, A. & Fellows, L. K. Compensatory striatal–cerebellar connectivity in mild–moderate Parkinson's disease. *NeuroImage Clin.* **10**, 54–62 (2016).

153.   Uddin, L. Q., Clare Kelly, A. M., Biswal, B. B., Castellanos, F. X. & Milham, M. P. Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Hum. Brain Mapp.* **30**, 10.1002/hbm.20531 (2009).

154.   Braak, H. & Braak, E. Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories. *Neurobiol. Aging* **18**, 351–357 (1997).

155.   Palmqvist, S. *et al.* Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nat. Commun.* **8**, (2017).

156.   Qi, H., Liu, H., Hu, H., He, H. & Zhao, X. Primary Disruption of the Memory-Related Subsystems of the Default Mode Network in Alzheimer's Disease: Resting-State Functional Connectivity MRI Study. *Front. Aging Neurosci.* **10**, 344–344 (2018).

157.   Grieder, M., Wang, D. J. J., Dierks, T., Wahlund, L.-O. & Jann, K. Default Mode Network Complexity and Cognitive Decline in Mild Alzheimer's Disease. *Front. Neurosci.* **12**, 770–770 (2018).

158. Nuttall, R., Pasquini, L., Scherr, M. & Sorg, C. Degradation in intrinsic connectivity networks across the Alzheimer's disease spectrum. *Alzheimers Dement. Amst. Neth.* **5**, 35–42 (2016).

159. Qi, Z. *et al.* Impairment and compensation coexist in amnestic MCI default mode network. *NeuroImage* **50**, 48–55 (2010).

160. Dickerson, B. C. *et al.* Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* **65**, 404–411 (2005).

161. Fleisher, A. S. *et al.* Resting-state BOLD networks versus task-associated functional MRI for distinguishing Alzheimer's disease risk groups. *NeuroImage* **47**, 1678–1690 (2009).

162. Filippini, N. *et al.* Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 7209–7214 (2009).

163. Andrews-Hanna, J. R., Smallwood, J. & Spreng, R. N. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann. N. Y. Acad. Sci.* **1316**, 29–52 (2014).

164. Gusnard, D. A., Akbudak, E., Shulman, G. L. & Raichle, M. E. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 4259–4264 (2001).

165. Qi, H., Liu, H., Hu, H., He, H. & Zhao, X. Primary Disruption of the Memory-Related Subsystems of the Default Mode Network in Alzheimer's Disease: Resting-State Functional Connectivity MRI Study. *Front. Aging Neurosci.* **10**, 344 (2018).

166. Vipin, A. *et al.* Cerebrovascular disease influences functional and structural network connectivity in patients with amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimers Res. Ther.* **10**, 82 (2018).

167. Bai, F. *et al.* Abnormal whole-brain functional connection in amnestic mild cognitive impairment patients. *Behav. Brain Res.* **216**, 666–672 (2011).

168. Busse, A., Angermeyer, M. C. & Riedel-Heller, S. G. Progression of mild cognitive impairment to dementia: a challenge to current thinking. *Br. J. Psychiatry* **189**, 399–404 (2006).

169.   Allegri, R. F., Glaser, F. B., Taragano, F. E. & Buschke, H. Mild cognitive impairment: Believe it or not? *Int. Rev. Psychiatry* **20**, 357–363 (2008).

170.   Wang, L. *et al.* Cerebrospinal Fluid Aβ42, Phosphorylated Tau181, and Resting-State Functional ConnectivityCSF Aβ42, Tau181, and Resting-State ConnectivityCSF Aβ42, Tau181, and Resting-State Connectivity. *JAMA Neurol.* **70**, 1242–1248 (2013).

171.   Li, K. *et al.* Aberrant functional connectivity network in subjective memory complaint individuals relates to pathological biomarkers. *Transl. Neurodegener.* **7**, 27–27 (2018).

172.   Yan, C. & Zang, Y. DPARSF: a MATLAB toolbox for 'pipeline' data analysis of resting-state fMRI. *Front. Syst. Neurosci.* **4**, 13 (2010).

173.   Wang, B. *et al.* Decreased Complexity in Alzheimer's Disease: Resting-State fMRI Evidence of Brain Entropy Mapping. *Front. Aging Neurosci.* **9**, 378–378 (2017).

174.   Yan, C.-G. *et al.* A Comprehensive Assessment of Regional Variation in the Impact of Head Micromovements on Functional Connectomics. *NeuroImage* **76**, 183–201 (2013).

175.   Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B. & Bandettini, P. A. The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage* **44**, 893–905 (2009).

176.   Ashburner, J. A fast diffeomorphic image registration algorithm. *NeuroImage* **38**, 95–113 (2007).

177.   Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L. & Petersen, S. E. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* **59**, 2142–2154 (2012).

178.   Calhoun, V. D., Adali, T., Pearlson, G. D. & Pekar, J. J. A method for making group inferences from functional MRI data using independent component analysis. *Hum. Brain Mapp.* **14**, 140–151 (2001).

179.   Calhoun, V. D., Liu, J. & Adali, T. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage* **45**, S163–72 (2009).

180.   Dipasquale, O. *et al.* High-Dimensional ICA Analysis Detects Within-Network Functional

Connectivity Damage of Default-Mode and Sensory-Motor Networks in Alzheimer's Disease. *Front.*

Hum. Neurosci. **9**, 43 (2015).

181.   Yu, Q. *et al.* Comparing brain graphs in which nodes are regions of interest or independent

components: A simulation study. *J. Neurosci. Methods* **291**, 61–68 (2017).

182.   Calhoun, V. D. & de Lacy, N. Ten Key Observations on the Analysis of Resting-state Functional

MR Imaging Data Using Independent Component Analysis. *Neuroimaging Clin. N. Am.* **27**, 561–579

(2017).

183.   Allen, E. A. *et al.* A Baseline for the Multivariate Comparison of Resting-State Networks. *Front.*

Syst. Neurosci. **5**, 2 (2011).

184.   *R: A language and environment for statistical computing.* (R   Foundation for Statistical

Computing, 2015).

185.   Yoav Benjamini & Yosef Hochberg. Controlling the false discovery rate: A practical and

powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B Methodol.* **57**, 289–300 (1995).

186.   Palmqvist, S., Mattsson, N., Hansson, O. & Alzheimer's Disease Neuroimaging Initiative.

Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission

tomography. *Brain J. Neurol.* **139**, 1226–1236 (2016).

187.   Fletcher, E. *et al.* Staging of amyloid β, t-tau, regional atrophy rates, and cognitive change in a

nondemented cohort: Results of serial mediation analyses. *Alzheimers Dement. Amst. Neth.* **10**, 382–

393 (2018).

188.   Canty, Angelo & Ripley, Brian. *boot: Bootstrap R (S-Plus) Functions*. (2017).

189.   Raschka, S. Model Evaluation, Model Selection, and Algorithm Selection in Machine Learning.

ArXiv181112808 Cs Stat (2018).

190.   Kenny, E. R., Blamire, A. M., Firbank, M. J. & O'Brien, J. T. Functional connectivity in cortical

regions in dementia with Lewy bodies and Alzheimer's disease. *Brain* **135**, 569–581 (2012).

191.   Wang, L. *et al.* Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. *NeuroImage* **31**, 496–504 (2006).

192.   Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R. & Buckner, R. L. Functional-anatomic fractionation of the brain's default network. *Neuron* **65**, 550–562 (2010).

193.   Zhu, X., Zhu, Q., Shen, H., Liao, W. & Yuan, F. Rumination and Default Mode Network Subsystems Connectivity in First-episode, Drug-Naive Young Patients with Major Depressive Disorder. *Sci. Rep.* **7**, 43105–43105 (2017).

194.   Du, Y. *et al.* Interaction among subsystems within default mode network diminished in schizophrenia patients: A dynamic connectivity approach. *Schizophr. Res.* **170**, 55–65 (2016).

195.   Blokland, G. A. M. *et al.* The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) consortium: A collaborative cognitive and neuroimaging genetics project. *Schizophr. Res.* doi:10.1016/j.schres.2017.09.024.

196.   Alexander, A. C. *et al.* Racial Differences in Posttraumatic Stress Disorder Vulnerability Following Hurricane Katrina Among a Sample of Adult Cigarette Smokers from New Orleans. *J. Racial Ethn. Health Disparities* **4**, 94–103 (2017).

197.   Hird, A. M. *et al.* Altered Functional Brain Connectivity in Mild Cognitive Impairment during a Cognitively Complex Car Following Task. *Geriatrics* **3**, (2018).

198.   Hillary, F. G. *et al.* Hyperconnectivity is a fundamental response to neurological disruption. *Neuropsychology* **29**, 59–75 (2015).

199.   Wang, P. *et al.* Aberrant intra- and inter-network connectivity architectures in Alzheimer's disease and mild cognitive impairment. **5**, 14824 (2015).

200.   Miles, T. P., Froehlich, T. E., Bogardus, S. T. & Inouye, S. K. Dementia and Race: Are There Differences Between African Americans and Caucasians? *J. Am. Geriatr. Soc.* **49**, 477–484 (2001).

201.   Braak, H. & Del Tredici, K. Spreading of Tau Pathology in Sporadic Alzheimer's Disease Along Cortico-cortical Top-Down Connections. *Cereb. Cortex N. Y. N 1991* **28**, 3372–3384 (2018).

202. Sun, Y. *et al.* Abnormal functional connectivity in patients with vascular cognitive impairment, no dementia: A resting-state functional magnetic resonance imaging study. *Behav. Brain Res.* **223**, 388–394 (2011).

203. Alosco, M. L. *et al.* A Clinicopathological Investigation of White Matter Hyperintensities and Alzheimer's Disease Neuropathology. *J. Alzheimers Dis. JAD* **63**, 1347–1360 (2018).

204. Zahodne, L. B. *et al.* Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. *Curr. Alzheimer Res.* **12**, 632–639 (2015).

205. Krieger, N. & Sidney, S. Racial discrimination and blood pressure: the CARDIA Study of young black and white adults. *Am. J. Public Health* **86**, 1370–1378 (1996).

206. Sawyer, P. J., Major, B., Casad, B. J., Townsend, S. S. M. & Mendes, W. B. Discrimination and the stress response: psychological and physiological consequences of anticipating prejudice in interethnic interactions. *Am. J. Public Health* **102**, 1020–1026 (2012).

207. Berger, M. & Sarnyai, Z. "More than skin deep": stress neurobiology and mental health consequences of racial discrimination. *Stress* **18**, 1–10 (2015).

208. Bisht, K., Sharma, K. & Tremblay, M.-È. Chronic stress as a risk factor for Alzheimer's disease: Roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress. *Neurobiol. Stress* **9**, 9–21 (2018).

209. Soares, J. M. *et al.* Stress Impact on Resting State Brain Networks. *PLOS ONE* **8**, e66500 (2013).

210. Kind, A. J. H. & Buckingham, W. R. Making Neighborhood-Disadvantage Metrics Accessible — The Neighborhood Atlas. *N. Engl. J. Med.* **378**, 2456–2458 (2018).

211. Misiura, M. B. *et al.* Race modifies default mode connectivity in Alzheimer's disease. *Transl. Neurodegener.* **9**, 8 (2020).

212. Chin, A. L., Negash, S. & Hamilton, R. Diversity and Disparity in Dementia: The Impact of Ethnoracial Differences in Alzheimer's Disease. *Alzheimer Dis. Assoc. Disord.* **25**, 187–195 (2011).

213. Komatsu, J. *et al.* Optimization of DARTEL Settings for the Detection of Alzheimer Disease. *Am. J. Neuroradiol.* **39**, 473 (2018).

214. Brown, P. J. *et al.* Frailty and Its Correlates in Adults With Late Life Depression. *Am. J. Geriatr. Psychiatry* **28**, 145–154 (2020).

215. Klunk, W. E. *et al.* Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. *J. Neurosci. Off. J. Soc. Neurosci.* **27**, 6174–6184 (2007).

216. Vitanova, K. S., Stringer, K. M., Benitez, D. P., Brenton, J. & Cummings, D. M. Dementia associated with disorders of the basal ganglia. *J. Neurosci. Res.* **97**, 1728–1741 (2019).

217. Johnson, K. A., Fox, N. C., Sperling, R. A. & Klunk, W. E. Brain Imaging in Alzheimer Disease. *Cold Spring Harb. Perspect. Med.* **2**, a006213 (2012).

218. Braak, H. & Braak, E. Alzheimer's disease affects limbic nuclei of the thalamus. *Acta Neuropathol. (Berl.)* **81**, 261–268 (1991).

219. Akiyama, H., Harrop, R., McGeer, P. L., Peppard, R. & McGeer, E. G. Crossed cerebellar and uncrossed basal ganglia and thalarnic diaschisis in Alzheimer's disease. *Neurology* **39**, 541 (1989).

220. Timmers, T. *et al.* Associations between quantitative [18F]flortaucipir tau PET and atrophy across the Alzheimer's disease spectrum. *Alzheimers Res. Ther.* **11**, 60 (2019).

221. Mosconi, L. & McHugh, P. F. FDG- and amyloid-PET in Alzheimer's disease: is the whole greater than the sum of the parts? *Q. J. Nucl. Med. Mol. Imaging Off. Publ. Ital. Assoc. Nucl. Med. AIMN Int. Assoc. Radiopharmacol. IAR Sect. Soc. Of* **55**, 250–264 (2011).

222. van den Heuvel, M. P. & Hulshoff Pol, H. E. Exploring the brain network: A review on resting-state fMRI functional connectivity. *Eur. Neuropsychopharmacol.* **20**, 519–534 (2010).

223. Badhwar, A. *et al.* Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimers Dement. Amst. Neth.* **8**, 73–85 (2017).

224. Damoiseaux, J. S. Resting-state fMRI as a biomarker for Alzheimer's disease? *Alzheimers Res. Ther.* **4**, 8–8 (2012).

225. Anticevic, A. *et al.* Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol. Psychiatry* **75**, 595–605 (2014).

226. Shen, B. *et al.* Altered putamen and cerebellum connectivity among different subtypes of Parkinson's disease. *CNS Neurosci. Ther.* **26**, 207–214 (2020).

227. Seidler, R. D., Noll, D. C. & Chintalapati, P. Bilateral basal ganglia activation associated with sensorimotor adaptation. *Exp. Brain Res.* **175**, 544–555 (2006).

228. McLaren, D. G. *et al.* Tracking cognitive change over 24 weeks with longitudinal functional magnetic resonance imaging in Alzheimer's disease. *Neurodegener. Dis.* **9**, 176–186 (2012).

229. Huijbers, W. *et al.* Amyloid-β deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. *Brain J. Neurol.* **138**, 1023–1035 (2015).

230. Braskie, M. N. *et al.* Increased fMRI signal with age in familial Alzheimer's disease mutation carriers. *Neurobiol. Aging* **33**, 424.e11-424.e21 (2012).

231. Son, S.-J., Kim, J. & Park, H. Structural and functional connectional fingerprints in mild cognitive impairment and Alzheimer's disease patients. *PLOS ONE* **12**, e0173426 (2017).

232. Thong, J. Y. J. *et al.* Abnormalities of cortical thickness, subcortical shapes, and white matter integrity in subcortical vascular cognitive impairment. *Hum. Brain Mapp.* **35**, 2320–2332 (2014).

233. Abraham, H. M. A. *et al.* Cardiovascular risk factors and small vessel disease of the brain: Blood pressure, white matter lesions, and functional decline in older persons. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* **36**, 132–142 (2016).

234. Mortamais, M., Artero, S. & Ritchie, K. Cerebral white matter hyperintensities in the prediction of cognitive decline and incident dementia. *Int. Rev. Psychiatry Abingdon Engl.* **25**, 686–698 (2013).

235. Brickman, A. M. *et al.* Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. *Arch. Neurol.* **69**, 1621–1627 (2012).

236. De Marco, M., Manca, R., Mitolo, M. & Venneri, A. White Matter Hyperintensity Load Modulates Brain Morphometry and Brain Connectivity in Healthy Adults: A Neuroplastic Mechanism? *Neural Plast.* **2017**, 4050536 (2017).

237. Young, V. G., Halliday, G. M. & Kril, J. J. Neuropathologic correlates of white matter hyperintensities. *Neurology* **71**, 804 (2008).

238. Elliott, R. Executive functions and their disorders: Imaging in clinical neuroscience. *Br. Med. Bull.* **65**, 49–59 (2003).

239. Morris, J. C. *et al.* Assessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer Disease. *JAMA Neurol.* **76**, 264–273 (2019).

240. Barnes, L. L. *et al.* Racial differences in the progression of cognitive decline in Alzheimer disease. *Am J Geriatr Psychiatry* **13**, (2005).

241. Morris, J. C. *et al.* Assessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer DiseaseAssessment of Racial Disparities in Biomarkers for Alzheimer Disease. *JAMA Neurol.* **76**, 264–273 (2019).

242. Pruim, R. H. R. *et al.* ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *NeuroImage* **112**, 267–277 (2015).

243. Garrett, S. L. *et al.* Racial Disparity in Cerebrospinal Fluid Amyloid and Tau Biomarkers and Associated Cutoffs for Mild Cognitive Impairment. *JAMA Netw. Open* **2**, e1917363–e1917363 (2019).

244. Buchhave, P. *et al.* Cerebrospinal Fluid Levels ofβ-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia. *Arch. Gen. Psychiatry* **69**, 98–106 (2012).

245. Oberhuber, M. *et al.* Functionally distinct contributions of the anterior and posterior putamen during sublexical and lexical reading. *Front. Hum. Neurosci.* **7**, 787–787 (2013).

246. Cacciola, A. *et al.* A Connectomic Analysis of the Human Basal Ganglia Network. *Front. Neuroanat.* **11**, 85–85 (2017).

247. Purves, D, Augustine, GJ & Fitzpatrick, D. *Neuroscience 2nd edition*. (Sinauer Associates, 2001).

248. Wang, X.-N. *et al.* Abnormal organization of white matter networks in patients with subjective cognitive decline and mild cognitive impairment. *Oncotarget* **7**, 48953–48962 (2016).

249. Ishibashi, M., Kimura, N., Aso, Y. & Matsubara, E. Effects of white matter lesions on brain perfusion in patients with mild cognitive impairment. *Clin. Neurol. Neurosurg.* **168**, 7–11 (2018).

250. Tao, Y. *et al.* The Structural Connectivity Pattern of the Default Mode Network and Its Association with Memory and Anxiety. *Front. Neuroanat.* **9**, 152–152 (2015).

251. Roseborough, A., Ramirez, J., Black, S. E. & Edwards, J. D. Associations between amyloid β and white matter hyperintensities: A systematic review. *Alzheimers Dement.* **13**, 1154–1167 (2017).

252. Teixeira, S. & Zuberi, A. Mapping the Racial Inequality in Place: Using Youth Perceptions to Identify Unequal Exposure to Neighborhood Environmental Hazards. *Int. J. Environ. Res. Public. Health* **13**, 844 (2016).

253. Arnsten, A. F. T. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat. Rev. Neurosci.* **10**, 410–422 (2009).

254. Arnsten, A. F. T., Raskind, M. A., Taylor, F. B. & Connor, D. F. The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Stress Resil.* **1**, 89–99 (2015).

255. Wang, S. *et al.* Stress and the brain: Perceived stress mediates the impact of the superior frontal gyrus spontaneous activity on depressive symptoms in late adolescence. *Hum. Brain Mapp.* **40**, 4982–4993 (2019).

256. Harrell, J. P., Hall, S. & Taliaferro, J. Physiological responses to racism and discrimination: an assessment of the evidence. *Am. J. Public Health* **93**, 243–248 (2003).

257. Cohen, A. D. *et al.* Fluid and PET biomarkers for amyloid pathology in Alzheimer's disease. *Dis. Signat. Biomarkersindicators Neurodegener.* **97**, 3–17 (2019).

258. Xiang, J., Guo, H., Cao, R., Liang, H. & Chen, J. An abnormal resting-state functional brain network indicates progression towards Alzheimer's disease. *Neural Regen. Res.* **8**, 2789–2799 (2013).

259. Antoine, N. *et al.* Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum. Brain Mapp.* **40**, 5330–5340 (2019).

260. Yuan, B. *et al.* Differential effects of APOE genotypes on the anterior and posterior subnetworks of default mode network in amnestic mild cognitive impairment. *J. Alzheimers Dis.* **54**, 1409–1423 (2016).

261. Ferreri, F. *et al.* Sensorimotor cortex excitability and connectivity in Alzheimer's disease: A TMS-EEG Co-registration study. *Hum. Brain Mapp.* **37**, 2083–2096 (2016).

262. Clark, C. M. *et al.* Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA* **305**, (2011).

263. Jiang, Y. *et al.* Alzheimer's Biomarkers are Correlated with Brain Connectivity in Older Adults Differentially during Resting and Task States. *Front. Aging Neurosci.* **8**, 15 (2016).

264. Ford, G., Haley, W., Thrower, S., West, C. & Harrell, L. Utility of Mini-Mental State Exam scores in predicting functional impairment among white and African American dementia patients. *J. Gerontol.* **51A**, 185–188 (1996).

265. Schweizer, T. A., Al-Khindi, T. & Macdonald, R. L. Mini-Mental State Examination versus Montreal Cognitive Assessment: Rapid assessment tools for cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *J. Neurol. Sci.* **316**, 137–140 (2012).

266. Luo, X. *et al.* Intrinsic functional connectivity alterations in cognitively intact elderly APOE ε4 carriers measured by eigenvector centrality mapping are related to cognition and CSF biomarkers: a preliminary study. *Brain Imaging Behav.* **11**, 1290–1301 (2017).

267. Sripada, R. K., Swain, J. E., Evans, G. W., Welsh, R. C. & Liberzon, I. Childhood Poverty and Stress Reactivity Are Associated with Aberrant Functional Connectivity in Default Mode Network. *Neuropsychopharmacology* **39**, 2244–2251 (2014).

268. Lipira, L. *et al.* Religiosity, Social Support, and Ethnic Identity: Exploring 'Resilience Resources' for African-American Women Experiencing HIV-Related Stigma. *J. Acquir. Immune Defic. Syndr. 1999* **81**, 175–183 (2019).

269.   Morese, R., Lamm, C., Bosco, F. M., Valentini, M. C. & Silani, G. Social support modulates the neural correlates underlying social exclusion. *Soc. Cogn. Affect. Neurosci.* **14**, 633–643 (2019).

270.   McAleese, K. E. *et al.* Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathol. Commun.* **3**, 60–60 (2015).

271.   Cechetto, D. F., Hachinski, V. & Whitehead, S. N. Vascular risk factors and Alzheimer's disease. *Expert Rev. Neurother.* **8**, 743–750 (2008).

272.   Alber, J. *et al.* White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. *Alzheimers Dement. N. Y. N* **5**, 107–117 (2019).

273.   Pickett, E. R., Kuniholm, E., Protopapas, A., Friedman, J. & Lieberman, P. Selective speech motor, syntax and cognitive deficits associated with bilateral damage to the putamen and the head of the caudate nucleus: a case study. *Neuropsychologia* **36**, 173–188 (1998).

274.   Levy, R. & Dubois, B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* **16**, 916–928 (2006).

275.   Nebel, R. A. *et al.* Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimers Dement. J. Alzheimers Assoc.* **14**, 1171–1183 (2018).

276.   Blair, C. & Raver, C. C. Poverty, Stress, and Brain Development: New Directions for Prevention and Intervention. *Acad. Pediatr.* **16**, S30–S36 (2016).

277.   Aiken-Morgan, A. T., Gamaldo, A. A., Sims, R. C., Allaire, J. C. & Whitfield, K. E. Education Desegregation and Cognitive Change in African American Older Adults. *J. Gerontol. Ser. B* **70**, 348–356 (2015).

278.   Gong, N.-J., Wong, C.-S., Chan, C.-C., Leung, L.-M. & Chu, Y.-C. Aging in deep gray matter and white matter revealed by diffusional kurtosis imaging. *Neurobiol. Aging* **35**, 2203–2216 (2014).

279.   Donnez, J. & Dolmans, M.-M. Uterine fibroid management: from the present to the future. *Hum. Reprod. Update* **22**, 665–686 (2016).