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RESEARCH ARTICLE

Neuroimaging correlates of Alzheimer's disease biomarker concentrations in a racially diverse high-risk cohort of middle-aged adults

Maria Misiura[1,2] | **Chinkuli Munkombwe**[3] | **Kay Igwe**[4] | **Danielle D. Verble**[5] | **Kelly D. S. Likos**[5] | **Lex Minto**[1] | **Alexandria Bartlett**[1] | **Henrik Zetterberg**[6,7,8,9,10,11] | **Jessica A. Turner**[12] | **Vonetta M. Dotson**[1,13] | **Adam M. Brickman**[4,14] | **William T. Hu**[15] | **Whitney Wharton**[5]

[1]Department of Psychology, Georgia State University, Atlanta, Georgia, USA

[2]Tri-Institutional Center for Translational Research in Neuroimaging & Data Science, Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, Georgia, USA

[3]Neuroscience Institute, Georgia State University, Atlanta, Georgia, USA

[4]Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Gertrude H. Sergievsky Center, and Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA

[5]Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Georgia, USA

[6]The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Mölndal and Gothenburg, University of Gothenburg, Gothenburg, Sweden

[7]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[8]Department of Neurodegenerative Disease, UCL Institute of Neurology, UCL Queen Square Institute of Neurology, London, UK

[9]UK Dementia Research Institute at UCL, Maple House, London, UK

[10]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

[11]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

[12]Department of Psychiatry and Mental Health, College of Medicine, Ohio State University, Columbus, Ohio, USA

[13]Gerontology Department, Georgia State University, Atlanta, Georgia, USA

[14]Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, New York, USA

[15]Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, New Jersey, USA

Correspondence
Maria Misiura, Department of Psychology, Georgia State University, Atlanta, GA, USA.
Email: mmisiura1@gsu.edu

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Abstract

INTRODUCTION: In this study, we investigated biomarkers in a midlife, racially diverse, at-risk cohort to facilitate early identification and intervention. We examined neuroimaging measures, including resting state functional magnetic resonance imaging (fMRI), white matter hyperintensity vo (WMH), and hippocampal volumes, alongside cerebrospinal fluid (CSF) markers.

METHODS: Our data set included 76 cognitively unimpaired, middle-aged, Black Americans (N = 29, F/M = 17/12) and Non-Hispanic White (N = 47, F/M = 27/20)

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individuals. We compared cerebrospinal fluid phosphorylated tau141 and amyloid beta (Aβ)42 to fMRI default mode network (DMN) subnetwork connectivity, WMH volumes, and hippocampal volumes.

RESULTS: Results revealed a significant race × Aβ42 interaction in Black Americans: lower Aβ42 was associated with reduced DMN connectivity and increased WMH volumes regions but not in non-Hispanic White individuals.

DISCUSSION: Our findings suggest that precuneus DMN connectivity and temporal WMHs may be linked to Alzheimer's disease risk pathology during middle age, particularly in Black Americans.

KEYWORDS
Alzheimer's disease, cerebrospinal fluid, cerebrovascular disease, functional connectivity, neuroimaging

Highlights

- Cerebrospinal fluid (CSF) amyloid beta (Aβ)42 relates to precuneus functional connectivity in Black, but not White, Americans.
- Higher white matter hyperintensity volume relates to lower CSF Aβ42 in Black Americans.
- Precuneus may be a hub for early Alzheimer's disease pathology changes detected by functional connectivity.

1 | BACKGROUND

Black Americans are 64% more likely to develop Alzheimer's disease (AD) compared to non-Hispanic White (NHW) Americans.[1,2] It is well established that race is a social construct and there is a need to understand how sociocultural factors congregate within these groups to generate biological differences in health outcomes.[3] Defining AD biomarker cutoffs and trajectories across ethno-racial groups is an imperative step toward eliminating health disparities in diagnostics, disease progression, clinical trial enrollment, and prescription practices. AD biomarkers from both functional[4] and structural[5] magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) studies[6,7] show that Black American individuals may exhibit a unique AD biomarker profile.

The default mode network (DMN) is the most well-characterized functional imaging network in AD research,[8,9] and individuals with AD exhibit a more rapid decline in DMN connectivity than those with normal aging.[10,11] DMN functional connectivity abnormalities have been reported in the presence of amyloid beta (Aβ)42 pathology in preclinical and dementia cohorts as measured by CSF[12,13] and Pittsburgh compound B (PiB) positron emission tomography (PET) imaging.[14–16] Because functional network changes typically precede symptoms in AD, some have proposed the use of longitudinal functional MRI (fMRI) as a biomarker of AD.[17,18] However, despite the large number of studies examining the DMN, most samples are from primarily NHW populations.[19] Models of functional connectivity may not be generalizable across ethno-racial groups. We previously identified that among older Black Americans with and without AD, greater connectivity between the precuneus and regions of the dorsomedial subsystem of the DMN was related to increased CSF total tau, lower CSF Aβ42, and worse cognitive performance[20] (Black American = [43 F/29 M], NHW = [35 F/37 M], M_{Age} = 70.05, standard deviation [SD]$_{Age}$ = 7.67, Atlanta, GA). If we are to use DMN connectivity as a biomarker for AD, we must ensure that it generalizes across ethno-racial groups, particularly those most affected by AD.

In addition to fMRI, structural MRI identifies regions of atrophy related to AD.[21,22] White matter hyperintensity (WMH) volume is typically considered a marker of small vessel cerebrovascular disease[23] and is associated with the risk and progression of dementia.[24–26] Black Americans have higher rates of systemic vascular conditions including hypercholesterolemia,[27] hypertension,[28] and type 2 diabetes,[29] all of which are associated with white matter abnormalities.[30–33] Studies show that Black Americans have larger WMH volumes than their NHW counterparts.[34,35] Howell et al. found that in older individuals on the AD spectrum, increases in WMH volume were associated with poorer cognitive performance in Black Americans than in NHW participants.[6] Studies that investigated lobe-specific or regional WMH volumes found that parietal lobe volumes are most consistently associated with dementia,[36] and that parietal WMHs were more strongly associated with cortical thinning in areas that overlap with typical

patterns on AD neurodegeneration.[37] Few studies have investigated regional WMH volumes with an eye toward potential ethno-racial disparities.

Hippocampal atrophy is perhaps the most common MRI finding in individuals with AD.[38] Hippocampal volume relates to both CSF Aβ42[39] and CSF total and hyperphosphorylated tau (p-tau).[40] Factors associated with lower hippocampal volume, aside from AD pathology, include racial discrimination,[41] stress,[42] and vascular conditions[43] (e.g., hypertension[44] and type 2 diabetes[45]), all of which are reported to be more prevalent in Black Americans.[46–51] While there is little evidence that hippocampal atrophy occurs as early as midlife in the presence of AD pathology,[52,53] the reported ethnocultural disparities and the relatively few studies comparing hippocampal volume and CSF AD biomarkers in midlife warrant further analysis in diverse cohorts.

Recently, the field has embraced the need to analyze AD biomarkers in diverse cohorts to reduce health disparities. The "Black American" ethno-racial identity is a useful, yet simplistic, indicator of a typical conglomeration of factors including cardiovascular conditions, lower educational quality, apolipoprotein E (*APOE*) ε4 status, and lower socioeconomic status, that place Black Americans at a greater risk for AD. In this study, we compare DMN connectivity, regional WMH volumes, and hippocampal volumes to CSF markers of AD in a midlife cohort of racially diverse individuals with a family history of AD.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed literature using traditional (e.g., PubMed) sources. We know that Black Americans are at an increased risk of developing Alzheimer's disease (AD), but if racial differences related to imaging modalities exist is unclear. We investigated whether there is consistency in the reported relationships among cerebrospinal fluid (CSF) markers of AD and imaging.
2. **Interpretation**: Evidence suggested that there would be differences in relationships between CSF and neuroimaging modalities between races, but studies investigating ethno-racial differences and neuroimaging are limited in preclinical and at-risk populations.
3. **Future directions**: The article proposes a framework for the generation of new hypotheses and the conduct of additional studies. Examples include further understanding: (a) the relationships between amyloid beta 42 and functional connectivity even in middle age; (b) the role of race in the modification of CSF to neuroimaging biomarker relationships; and (c) if white matter hyperintensities and functional neuroimaging measures are independently related CSF markers of AD.

2 | METHODS

2.1 | Participants

Participants included cognitively unimpaired, middle-aged, self-identified Non-Hispanic Black and NHW Americans with a parental history of AD[54] enrolled in the Association Between Cardiovascular Risk and Preclinical Alzheimer's Disease Pathology (ASCEND) study (Black Americans = 29, NHW = 47, PI Wharton). Full cohort demographics are displayed in Table 1. None of the individuals we enrolled were bilingual, and none identified as Hispanic. As previously described, we enrolled 82 middle-aged to older adult children of persons with AD (median age for Black Americans = 58, NHW = 60). AD diagnosis of family member was either autopsy confirmed or probable AD as defined by National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria and verified using the validated Dementia Questionnaire (DQ) and medical records when available. Participants were recruited from the Emory Alzheimer's Disease Research Center (ADRC) clinical cohort, physician referral, and through community events and received $100 compensation.

Baseline results and methods have been described previously,[54] but briefly, participants underwent a detailed interview for demographic information, medical and medication history including vascular risk factors (coronary artery disease, congestive heart failure, atrial fibrillation, hypertension, hyperlipidemia, diabetes, suspected transient ischemic attack) and other medical comorbidities (e.g., cancer). Participants had a biological parent with AD and were 45 to 65 years old at baseline. Exclusion criteria included significant neurologic disease, history of significant head trauma, major untreated depression, history of alcohol or substance abuse, and current diagnosis of AD or mild cognitive impairment. Twenty Black participants underwent lumbar puncture (LP), and of these participants, 16 of them also underwent an MRI. Reasons for fluctuating participant numbers are that individuals who have a contraindication for MRI may still be eligible for an LP, and LPs are occasionally unsuccessful. In Table S1 in supporting information, we have included the demographic makeup of individuals with CSF, LP, and MRI data.

2.2 | CSF collection

CSF was collected after an 8-hour overnight fast and according with the International Society for Biological and Environmental Repositories *Best Practices* guidelines.[55] Approximately 22 mL of CSF was collected using sterile polypropylene collection tubes. Participants underwent LP to collect CSF for Aβ and tau, and markers of vascular dysfunction and inflammatory cytokines and chemokines, as previously described.[54] Participants also underwent blood draw for analysis of (1) RAS function, including angiotensin-converting enzyme activity, (2) plasma inflammatory markers, and (3) *APOE* genotyping. CSF Aβ40, Aβ42, and p-tau concentrations were measured by Lumipulse technology (Fujirebio).[56,57] Samples were assayed in two batches by experienced and board-certified laboratory technicians. Intra-assay coefficients of variation were < 10% for all three analytes.

TABLE 1 Demographic data and biomarker levels.

	Black American ($n = 29$)	Non-Hispanic White ($n = 47$)
Age	60.1 ± 7.8	58.5 ± 6.1
Sex		
%Male/%Female	39.62/60.38	44.07/55.93
APOE ε4 (%)	38.5%	36.8%
CSF Aβ42	712 ± 162	700 ± 197
CSF t-tau	219 ± 96.4	333 ± 176**
CSF p-tau	39.1 ± 14.12	52.73 ± 21.98**
Hippocampal volume, cm^3	7.36 ± 0.62	7.68 ± 0.85
History of diabetes (%)	7.4%*	0%
History of hypertension (%)	57.1%*	34.00%
History of hyperlipidemia (%)	45%	45.9%
Total cardiovascular risk score (%)	0 = 25%/1 = 35%/ 2 = 35%/3 = 5%	0 = 37.8%/1 = 37.8%/ 2 = 24.4%/3 = 0%
WMH volume	3.10 ± 2.80	1.89 ± 0.78
National Area Deprivation Index	57 ± 24.17**	33.1 ± 22.05
Highest level of completed education (%)	15/41/44	18/38/44
High school or GED/ college/postgraduate		

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E: CSF, cerebrospinal fluid; GED, General Educational Development; p-tau, phosphorylated tau; SD, standard deviation; t-tau, total tau; WMH, white matter hyperintensity.
*= significantly different between groups at $p < 0.05$, **$p < 0.001$.

2.3 | Cardiovascular risk score

Using an approach described in previous analyses, we created a cardiovascular risk score to understand the relationship between cardiovascular risk factors and our variables of interest.[6,20] We created this score by coding presence of three common cardiovascular risk factors (hypertension, type 2 diabetes, hyperlipidemia) with either a "0" for not present, or "1" for present. We then summed the scores for a total cardiovascular risk score (minimum 0, maximum 3). Table S2 in supporting information includes the number of individuals with all combinations of cardiovascular conditions.

2.4 | Area Deprivation Index

We generated national Area Deprivation Index (ADI) scores as a proxy measure of socio-economic status using the Neighborhood Atlas.[58] Scores were generated from participant residential zip codes.

2.5 | Neuroimaging data

All participants were scanned on a MAGNETOM PrismaFit 3T MRI machine at the Emory Center for Systems Imaging. Scanning protocol included a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo sequence (repetition time [TR]/inversion time [TI]/echo time [TE] = 2300/800/2.89msec, flip angle = 8°, matrix = 256 × 256 × 176, and voxel size = 1 × 1 × $1mm^3$), a 4.25-minute eyes-open resting state fMRI scan (TR/TE = 3000 ms/32 ms, flip angle = 90°, field of view [FOV] = 200 × 200 mm^2, acquisition matrix = 220 × 220 × 144, voxel size = 2 × 2 × 2 mm^3, slice = 48, time point = 170), and a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE = 2480 ms/364 ms, flip angle = 90°, FOV = 250 × 250 mm^2, acquisition matrix = 250 × 250 × 160, voxel size = 1 × 1 × 1 mm^3, slice = 160).

2.6 | fMRI data preprocessing

We used a standard preprocessing pipeline using the DPARSFA toolbox.[59] The first 10 time points were removed, scans were slice time corrected, manually reoriented where necessary, realigned for head motion, normalized to Montreal Neurological Institute space, and smoothed using the DARTEL algorithm.[60,61] We then performed nuisance covariate regression (Friston's 24 parameter head motion regressors, CSF, white matter). We further removed motion confounds using ICA-AROMA[62] and applied a high-pass filter. We performed a seed-based analysis using the regions described by Andrews-Hanna et al.[63] in the three DMN subnetworks, namely, (1) the medial frontal and temporal lobe subsystem (temporal pole [TP], temporal parietal junction [TPJ], lateral temporal cortex [LTC], dorsomedial prefrontal cortex [dmPFC], and anterior medial prefrontal cortex [amPFC]), (2) the medial temporal lobe (MTL) subsystem (hippocampal formation, parahippocampal cortex, retrosplenial cortex, posterior inferior parietal lobule, ventromedial prefrontal cortex), and (3) the midline core (posterior cingulate and precuneus). As we were interested in precuneus to dorsomedial subsystem connectivity, we used five measures of pairwise connectivity between the precuneus and the following regions: amPFC, dmPFC, TPJ, LTC, and temporal pole, depicted in Figure 1.

2.7 | Regional WMH analysis

Regional WMH volumes were derived from T2-weighted FLAIR images.[64] Briefly, each participant's FLAIR image was brain extracted and intensity normalized. Images were then processed 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.

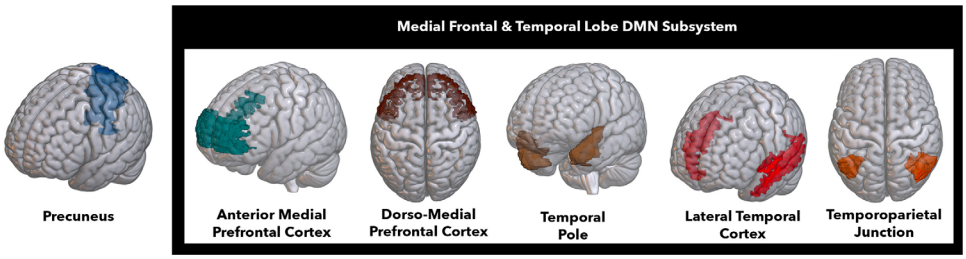

FIGURE 1 Regions of interest for the functional connectivity analysis. DMN, default mode network.

2.8 | Hippocampal volumes

T1-weighted images were processed with FreeSurfer (version 6).[65] We obtained hippocampal and total intracranial volume and calculated hippocampal volume as a proportion of total intracranial volume.

2.9 | Statistical analyses

We constructed three separate multiple multivariate regression models, one for each modality: functional connectivity, hippocampal volumes, and WMH volumes. Outcome variables for the functional connectivity models were precuneus to dmPFC, TPJ, LTC, TP, and amPFC. The independent variables were race, CSF Aβ42, and CSF p-tau, and covariates were sex, age, and mean framewise displacement (functional connectivity models only). We included race × CSF Aβ42, and race × p-tau interaction terms. We corrected for multiple comparisons using a Bonferroni correction in the "p.adjust" package in R and report the corrected *p*-values in the results table.[66] Our regression results depict only individuals who had complete data for our variables of interest; thus, sample size may vary marginally for each regression analysis.

Because we did not have statistical power to include all our variables of interest in one model, we conducted follow-up analyses to determine whether any risk factor variables associated with race that could potentially explain any racial differences that we identified. In these models, we added ADI, *APOE* ε4 status, and cardiovascular risk score.

3 | RESULTS

3.1 | Functional connectivity

Summary results of the functional connectivity analyses are displayed in Table 2 and Figure 2.

3.2 | Precuneus to amPFC connectivity

There was a significant race x Aβ42 interaction ($B = -0.001$, $t[0.29, 45] = -2.29$, $P = 0.04$). Lower Aβ42 levels were associated with lower connectivity, but only for Black American participants (Black Americans: $B = 0.001$, $t[4,11] = 2.39$, $P = 0.04$, NHW: $B = -0.0001$, $t[4,47] = 0.64$, $P = 0.62$). There was not a significant main effect or interaction for p-tau. Full model results are included in Table S3 in supporting information.

3.3 | Precuneus to TP connectivity

There was a significant race × Aβ42 interaction ($B = -0.001$, $t[6, 45] = -2.29$, $P = 0.03$). Lower Aβ42 levels were associated with lower connectivity, but only for Black American participants (Black Americans: $B = 0.001$, $t[4,11] = 1.98$, $p = 0.04$, NHW: $B = -0.0001$, $t[4,47] = -1.37$, $P = 0.18$). There was not a significant main effect or interaction for p-tau. Full model results are included in Table S4 in supporting information.

3.4 | Precuneus to TPJ connectivity

Lower Aβ42 levels were associated with lower connectivity (main effect of Aβ42, $B = 0.002$, $t[0.29, 45] = 2.57$, $P = 0.01$). There was a significant race × Aβ42 interaction ($B = -0.001$, $t[0.29, 45] = -2.22$, $P = 0.03$) such that within Black participants, lower Aβ42 was related to lower connectivity (Black Americans: $B = 0.001$, $t[4,11] = 1.06$, $P = 0.31$, NHW: $B = 0.001$, $t[4,47] = 0.39$, $P = 0.70$), but this relationship within group was not statistically significant. There was not a significant main effect or interaction for p-tau. Full model results are included in Table S5 in supporting information.

3.5 | Precuneus to dmPFC

Lower Aβ42 levels were associated with lower connectivity (main effect of Aβ42, $B = 0.002$, $t[0.29, 45] = 2.57$, $P = 0.01$). There was a significant race × Aβ42 interaction ($B = -0.001$, $t[0.29, 45] = -2.22$, $P = 0.03$) such that within Black participants, lower Aβ42 was related to lower connectivity (Black Americans: $B = 0.001$, $t[4,11] = 1.06$, $P = 0.31$, NHW: $B = 0.001$, $t[4,47] = -1.64$, $P = 0.11$), but this relationship within group was not statistically significant. There was not a significant main effect or interaction for p-tau. Full model results are included in Table S6 in supporting information.

TABLE 2 Functional connectivity race × Aβ42 summary table.

Precuneus to lateral temporal cortex			
	Estimate	**CI**	***p***
Race	0.75	−0.30 to 0.85	0.15
Aβ42	0.00001	−0.20 to 0.32	0.31
Race × Aβ42	−0.001	−0.04 to 0.05	0.26
Black	0.001	−2.45	0.88
White	−0.0003	−0.001 to 0.0001	0.18
Precuneus to dmPFC			
	Estimate	**CI**	***p***
Race	1.02	0.20 to 1.92	**0.04**
Aβ42	0.001	0.0002 to 0.002	**0.06**
Race × Aβ42	−0.001	−0.003 to 0.001	**0.06**
Black	−0.0003	−0.003 to 0.002	0.8
White	−0.0001	−0.001 to 0.001	0.82
Precuneus to temporal parietal junction			
	Estimate	**CI**	***p***
Race	1.05	0.30 to 1.80	**0.01**
Aβ42	0.01	0.00 to 0.01	**0.02**
Race × Aβ42	−0.001	−0.002 to −0.0001	**0.03**
Black	0.001	−0.001 to 0.003	0.31
White	0.19	−0.15 to 0.53	0.27
Precuneus to temporal pole			
	Estimate	**CI**	***p***
Race	0.39	0.03 to 0.75	**0.04**
Aβ42	0	0.00 to 0.00	**0.04**
Race × Aβ42	0	−0.00 to −0.00	**0.03**
Black	0.001	0.0001 to 0.002	**0.05**
White	−0.0003	−0.001 to 0.0001	0.18
Precuneus to amPFC connectivity			
	Estimate	**CI**	***p***
Race	1.06	0.20 to 1.92	**0.02**
Aβ42	0.001	0.0002 to 0.002	**0.02**
Race × Aβ42	−0.001	−0.003 to −0.0002	**0.03**
Black	0.001	0.0001 to 0.002	**0.04**
White	−0.0001	−0.0014	0.62

Note: Bold text = significant at $P < 0.05$.
Abbreviations: Aβ, amyloid beta; aMPFC, anterior medial prefrontal cortex; CI, confidence interval, dmPFC, dorsomedial prefrontal cortex.

3.6 | Precuneus to LTC connectivity

There was not a significant main effect or interaction of race ($B = 0.75$, 1, $t[0.29, 45) = 1.36$, $P = 0.15$), Aβ42($B = 0.00001$, 1, $t[0.29, 45] = 0.11$, $P = 0.31$), or p-tau. Full model results are included in Table S7 in supporting information.

3.7 | White matter hyperintensities and AD CSF biomarkers

Summary results of the WMH analyses are displayed in Table 3 and Figure 3.

For parietal lobe WMH volumes, there was a race × Aβ42 interaction ($B = 0.002$, $t[5,38] = 2.55$, $P = 0.05$) such that within Black participants, lower levels of CSF Aβ42 were related to higher parietal lobe WMH volumes (Black Americans: $B = -0.17$, $t[2,14] = -1.35$, $P = 0.05$, NHW: $B = 0.00003$, $t[3,31] = 1.72$, $P = 0.47$). Additionally, we observed a significant race × Aβ42 occipital lobe WMH volumes ($B = 0.001$, $t[4,45] = 2.24$, $P = 0.05$, Black Americans: $B = -0.05$, $t[2,14] = -1.25$, $P = 0.05$, NHW: $B = 0.00003$, $t[3,31] = 1.72$, $P = 0.47$), and temporal lobe WMH volumes (Black Americans: $B = -0.18$, $t[2,14] = -1.89$, $P = 0.01$, NHW: $B = 0.0003$, $t[3,31] = 0.89$, $P = 0.52$) interaction. Condensed model results are displayed in Table 3, and full model results in Tables S8-11 in supporting information.

3.8 | Hippocampal volume and AD CSF biomarkers

There was not a statistically significant relationship between hippocampal volume and CSF Aβ42 and p-tau.

3.9 | analyses with ethno-racial comorbidities

In our follow-up analyses, cardiovascular risk score, ADI, and *APOE* ε4 status were not significantly related to our outcome variables of interest. Results are included in supplemental tables.

4 | DISCUSSION

The purpose of this study was to identify the relationships between AD CSF biomarkers and AD neuroimaging biomarkers in a middle-aged, cognitively normal cohort of individuals with a parental history of AD. We identified an interaction between AD CSF biomarker levels, precuneus functional connectivity, and WMHs such that CSF Aβ42 was more strongly correlated with lower connectivity and increased WMH volumes in Black participants than in NHW participants.

Functional neuroimaging measures were only related to AD CSF biomarkers in Black participants. More specifically, lower CSF Aβ42 in Black participants was related to lower connectivity between the posterior cingulate cortex (PCC)/precuneus and regions of the medial frontal DMN subsystem. By contrast, no significant relationship between AD CSF biomarkers and DMN connectivity was observed in NHW participants. Previous research using this subsystem approach identified connectivity alterations between the PCC and the frontal and temporal lobe subsystems in NHW individuals with AD.[20,67,68] Precuneus connectivity is typically lower in individuals with AD, and lower precuneus connectivity correlates with increased amyloid deposition.[69–71] The precuneus also seems to be an initial site of amy-

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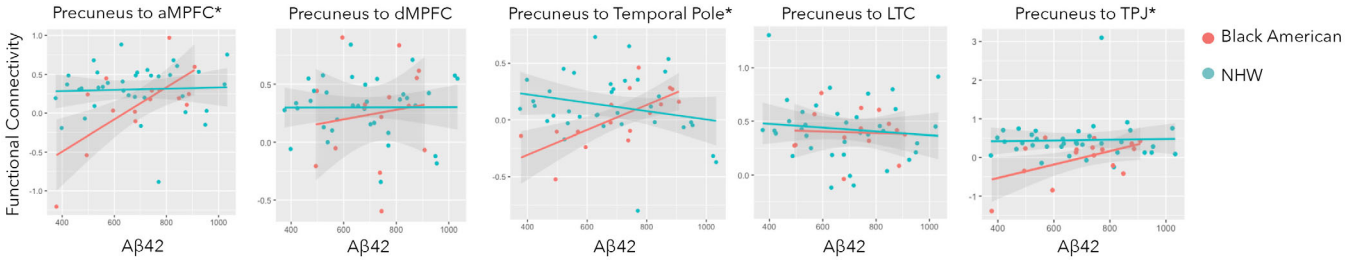

FIGURE 2 Functional connectivity to Aβ42. Red = Black American participants; Green = non-Hispanic White participants. Aβ, amyloid beta; amPFC, anterior medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; LTC, lateral temporal cortex; NHW, non-Hispanic White; PCC, posterior cingulate cortex; TPJ, temporal parietal junction.

TABLE 3 White matter hyperintensity race × Aβ42 summary table.

Frontal lobe WMH volumes			
	Estimates	**CI**	***p***
Race	0.17	−0.98 to 1.33	0.76
Aβ42	−0.001	−0.003 to 0.001	0.33
Race × Aβ42	0.001	−0.001 to 0.003	0.40
Black	−0.03	−0.11 to 0.04	0.25
White	<0.001	−0.0005 to 0.001	
Temporal lobe WMH volumes			
	Estimates	**CI**	***p***
Race	**−1.20**	**−1.89 to −0.52**	**0.001**
Aβ42	**− 0.00**	**−0.00 to −0.00**	**0.01**
Race × Aβ42	**0.00**	**0.00 to 0.00**	0.01
Black	**−0.18**	**− 0.01 to 0.005**	**0.050**
White	0.0003	−0.0001 to 0.0001	0.52
Parietal lobe WMH volumes			
	Estimates	**CI**	***p***
Race	0.14	−0.24 to 0.53	0.46
Aβ42	**−0.002**	**−0.003 to −0.002**	**<0.001**
Race × Aβ42	**0.002**	**0.002 to 0.003**	**<0.001**
Black	**−0.17**	**−0.01 to −0.0055**	**0.05**
White	0.00003	−0.0001 to 0.0001	0.47
Occipital lobe WMH volumes			
	Estimates	**CI**	***p***
Race	**−0.56**	**−0.96 to −0.16**	**0.007**
Aβ42	−0.0002	−0.00003 to 0.0000	0.18
Race × Aβ42	**0.001**	**0.0002 to 0.01**	**0.031**
Black	**−0.05**	**−0.01 to −0.0055**	**0.05**
White	0.00003	−0.0001 to 0.0001	0.47

Note: bold values indicate $p < 0.05$.
Abbreviations: Aβ, amyloid beta; CI, confidence interval; WMH, white matter hyperintensity.

loid accumulation in healthy aging.[72,73] Future research should investigate whether the CSF concentrations of Aβ42 are related to increased Aβ42 deposition in the precuneus and if there are ethno-racial–specific relationships between connectivity and regional amyloid deposition.

In an independent cohort of older Black Americans and NHW participants with and without AD, we previously identified race-related differences similar to those reported in the current work, but in the opposite direction:[20] greater DMN connectivity was related to *greater* AD biomarker burden between the precuneus and regions of the MTL/frontal subsystem among Black Americans. Comparisons across the two studies are difficult to make, as age and presence of AD change connectivity; however, the fact that we identified a race-related difference in connectivity to biomarker relationships in both cohorts does suggest that racial differences in brain biomarker relationships may be generalizable to other cohorts. A possible explanation for the fact that we observed the opposite relationship between two cohorts could be that the AD cohort included older adults, many of whom were on the dementia spectrum. Connectivity profiles can change throughout the lifetime, with some studies identifying both increased[74] and decreased[10,11] connectivity between default network nodes over the course of aging and AD. It could be that there are other regions more affected by amyloid in the later stages of the disease that then cause a compensatory mechanism within the DMN.[75,76]

Potential explanations for race-related differences may include differences in the prevalence of cardiovascular and sociocultural factors including stress and access to resources including health care, and, in our case, uneven distribution of sex across racial groups. Here we controlled for cardiovascular risk factors, *APOE* ε4 status, and socioeconomic status, and when we performed the same analyses within only women, we found that the relationships were still consistent. Potential explanations for these differences that we did not analyze include educational quality, diet, and exercise levels, which have been reported to affect connectivity and may show racial disparities, potentially due to access to resources and higher stress. Our sample is also unique in that participants were highly educated. Typically, only ≈ 26% of Black Americans across the United States have a bachelor's degree, compared to 41% in our sample. It is possible that we would see even more pronounced differences in brain biomarker relationships in a sample with a lower percentage of people with higher education. Black

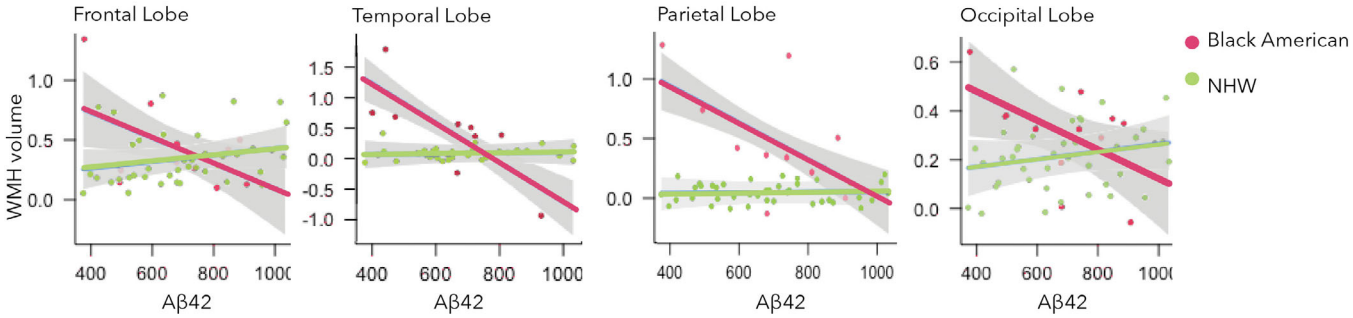

FIGURE 3 White matter hyperintensity volumes to Aβ42. Red = Black American participants; Green = non-Hispanic White participants. Aβ, amyloid beta; WMH, white matter hyperintensity.

Americans, particularly females, typically experience a greater number of adverse childhood experiences. We did not account for this in our analysis, which could explain some of the racial differences we identified.

4.1 | White matter hyperintensity volumes

This study is one of a few to include both WMHs and AD CSF biomarkers, particularly with attention to regional specificity, in a racially diverse, middle-aged cohort at high risk for AD by virtue of parental history. We identified a relationship between CSF Aβ levels and WMHs such that within cognitively healthy Black Americans, lower CSF Aβ42 was associated with increased WMH volumes in the parietal, temporal, and occipital lobes. We did not identify these same relationships in NHW participants. There is growing evidence that amyloid itself can cause WMHs, and lower CSF Aβ42 is often found to be related to increased WMH burden.[77,78]

Amyloid deposition in preclinical and healthy aging populations is not well characterized. CSF Aβ42 is typically lower in AD, but it does not always correlate with AD symptoms. Current models suggest that amyloid accumulation begins as early as 10 to 20 years before symptom onset, and that as Aβ reaches pathological loads, it plateaus and tau serves as a more accurate marker of disease trajectory. Although this is a small sample, the difference in our results for Black and NHW participants suggests that other health factors may underlie the disparate disease trajectories for these two groups.

Vascular health may play a role in the association between increased WMHs and AD CSF biomarkers observed in Black participants in this study. Black Americans demonstrate greater incidence and prevalence of cardiovascular diseases, including diabetes, hypertension, hypercholesterolemia, and obesity compared to NHW individuals.[51,79] Black Americans also have a greater WMH burden compared NHW individuals, a neuroimaging finding often considered to be an indicator of cerebrovascular burden and a finding we replicated in this cohort.[80,81] Although we did not observe a significant difference in amyloid deposition between groups in this study, higher vascular burden may result in a stronger relationship between amyloid deposition and WMH volumes for Black Americans.[82] Research has shown that cerebral amyloid angiopathy, which is the deposition of amyloid in cerebral blood vessels, may partially explain the relationship between amyloid and WMH volumes.[77,83] However, some study samples have neglected to show significant differences in cerebral amyloid angiopathy in Black Americans, underscoring the potential role of other determinants of health in dementia pathology for these groups.[84] While not measured in this study, it is possible that Black participants had increased vascular, compared to parenchymal, amyloid burden.

While we did not identify a significant relationship between cardiovascular risk score and our functional connectivity measures, it is possible that unique combinations of the vascular risk scores could explain some of the relationships that we identified. Hypertension, hyperlipidemia, and type 2 diabetes mellitus all predict worse AD brain biomarker outcomes; the combination of these factors and MRI biomarkers has not been thoroughly investigated. There is not a consensus about the effect of the combination of cardiovascular conditions on AD risk. Ruthirakuhan et al. found that hypertension + type 2 diabetes does not significantly increase AD risk more than hypertension alone.[85] Nakamura et al. reported that hypertension + hyperlipidemia did not increase dementia risk in a cohort of older Japanese adults.[86] Dyslipidemia and type 2 diabetes mellitus likely synergize to increase risk of AD, but we are unaware of an analysis of the effect of the combination of these two factors on brain biomarkers.[87] Research suggests that *APOE* ε4 status may modify the effects of these risk factors on AD risk, and should be considered in analysis of these factors.[88–90] Future analyses will investigate the effect of individual risk factors and all combinations of these risk factors on MRI and CSF biomarkers.

Disparities in central and peripheral vascular health are, in part, likely the result of lifetime exposure to systemic disadvantages in wealth, housing, education, neighborhood characteristics, access to health care, and racial discrimination.[91,92] These stressors appear to activate a physiological response in combination with epigenetic changes that "weather" the body and accelerate premature aging. For instance, chronic stress leads to hyperactivation of the hypothalamic–pituitary adrenal axis through the overproduction of glucocorticoids including cortisol which, over time, triggers neuroinflammation and hyperglycemia that collectively induce oxidative stress and ultimately

cause neuronal dysfunction.[93] High glucocorticoid concentrations are associated with increased Aβ deposition, which correlates with lower CSF Aβ42, and worse cognitive outcomes across measures of learning and memory.[94,95] Taken together, weathering may partially explain our finding of an association between elevated WMH volumes and low CSF Aβ42 in otherwise cognitively healthy Black participants but not NHW participants.

4.2 | Hippocampal volumes

The lack of relationships between hippocampal volumes and CSF Aβ42 and tau is not surprising. Atrophy in the presence of amyloid and tau typically does not occur until well after symptoms of AD have begun.[96–98] In AD, hyperphosphorylated tau—historically seen as the cause of MTL atrophy—typically emerges in the temporal lobe and then spreads from these MTL structures to the rest of the cortex.[99,100] Although the cognitively normal individuals in this study are at risk for AD, their pathology levels may not reach clinically significant thresholds required to cause atrophy. Our results support previous work that Black Americans do not exhibit higher rates of hippocampal atrophy, as we did not identify any racial differences in hippocampal volumes, and that these volumes do not typically exhibit vulnerability to AD pathology until late life.[36]

4.3 | Limitations

We were not able to analyze the interaction of race and sex on our variables of interest because of the uneven distribution of men across the two ethno-racial groups and individual cardiovascular conditions. Even though we still identified a significant interaction between races, the lower number of Black men limited our ability to analyze sex at a more granular level. We know that sex interacts with inflammatory pathways that can contribute to the development of AD,[101,102] and can affect the relationship between AD and WMH. As data collection and recruitment in this group are ongoing, we hope to explore the intersection of female sex and Black American race on the trajectory of the neuroimaging and CSF AD biomarkers.

Our sample size limited the number of explanatory variables that we could include in our analyses such as sex, adverse childhood experiences, and individual vascular conditions. Only individuals with complete datasets for each regression analysis were included in each model, further decreasing our sample size and limiting our statistical power. While our community-based recruitment methods help ensure that our samples are not collected out of convenience, we did not collect data from every stratum of society including individuals from rural areas, a high percentage of individuals with no higher education, bilingual individuals, and so on. Future work will analyze adverse childhood experiences, stress, and perceived discrimination and their relationship to the brain biomarker disparities we identified. Furthermore, multicohort meta-analyses and comparisons will allow us to investigate the generalizability of our findings.

Analysis of racial differences by category grossly generalizes across the diversity of the human condition. Race is likely a proxy measure for a variety of comorbid factors and experiences that converge to create an increased risk for dementia. However, because we can observe differences between these ethno-racial groups, further studies can investigate the nature of these disparities in hopes of then developing interventions to address unique needs of those most at risk for AD.

5 | CONCLUSION

CSF Aβ42 correlated with both precuneus functional connectivity and WMH volume in a cohort of Black Americans at risk for AD. This finding, consistent with relationships identified in individuals with AD, was not explained by potentially confounding variables such as ADI and cardiovascular risk factors alone. This work supports the notion that racial disparities in brain to biomarker relationships cannot be solely explained by disparities in vascular health, and that the degree to which someone experiences a combination of stressors more prevalent in their racial group may influence the relationship between amyloid and neurological function. Future research will investigate longitudinal changes in these biomarkers and their relationships to identify mechanisms linking amyloid to both neurological activity and WMH.

AUTHOR CONTRIBUTIONS

M. Misiura is the primary author of the manuscript responsible for much of the content, analytical design, neuroimaging analyses, and communication between authors. C. Munkombwe performed the WMH and CSF analyses and assisted with table consolidation. K. Igwe performed the WMH quantification under the supervision of A. M. Brickman. D. D. Verble assisted with data entry, participation recruitment, data collection, and data transfer. K. D. S. Likos assisted with data entry, participation recruitment, data collection, and data transfer. L. Minto authored portions of the manuscript. A. Bartlett authored portions of the manuscript. H. Zetterberg performed CSF analyses. J. Turner oversaw initial neuroimaging analyses. V. Dotson authored portions of this manuscript. A. M. Brickman oversaw the WMH quantification and provided feedback on manuscript drafts. W. T. Hu is a Wharton lab collaborator who assisted with data transfer and initial liasing between M. Misiura and W. Wharton. W. Wharton was the principal investigator of the ASCEND cohort study, provided feedback on manuscript and analyses, and authored portions of the manuscript.

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CONFLICT OF INTEREST STATEMENT

HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers,

Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). AMB holds an inventor a patent for white matter hyperintensity quantification (US patent# 9867566). Author disclosures are available in the supporting information. MM, CM, KI, DL, LM, AB, JAT, VMD, WTH, WW have nothing to disclose. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONSENT STATEMENT

This study was approved by the Emory IRB and participants consented to share their data.

CONSENT FOR PUBLICATION

All participants gave their consent for their de-identified data to be used for the analyses for this publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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