TOWARD A MORE REPRESENTATIVE BRAIN: THE IMPORTANCE AND ABSENCE OF DIVERSITY IN HUMAN NEUROSCIENCE RESEARCH ACROSS THE LIFESPAN

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ORIGINAL RESEARCH
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Collectivism Is Associated With Greater Neurocognitive Fluency in Older Adults

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Neuropsychological research has been limited in the representation of cultural diversity due to various issues, raising questions regarding the applicability of findings to diverse populations. Nonetheless, culture-dependent differences in fundamental psychological processes have been demonstrated. One of the most basic of these, self-construal (individualism, collectivism), is central to how many other differences are interpreted. Self-construals may have possible consequences on social interactions, emotions, motivation, and cognition. This study aimed to evaluate the impact of self-construal on neurocognitive functions in older adults. A total of 86 community-dwelling older adults 60 years and older were assessed with three common self-report measures of self-construal along individualism and collectivism (IC). A cognitive battery was administered to assess verbal and non-verbal fluency abilities. Latent profile analysis (LPA) was used to categorize individuals according to IC, and one-way analyses of covariance (ANCOVA), including relevant covariates (e.g., ethnicity, gender, linguistic abilities), were used to compare neurocognitive functions between individualists and collectivists. Collectivists outperformed individualists on left frontally-mediated measures of verbal fluency (action, phonemic) after controlling for relevant covariates, $F_{(1,77)} = 6.942$, $p = 0.010$, $\eta^2 = 0.061$. Groups did not differ on semantic fluency, non-verbal fluency, or attention/working memory (all $ps > 0.05$). These findings suggest a cognitive advantage in collectivists for verbal processing speed with an additional contribution of left frontal processes involved in lexicosemantic retrieval. Self-construal may provide a meaningful descriptor for diverse samples in neuropsychological research and may help explain other cross-cultural differences.

Keywords: executive function, cognition, culture, self-construal, verbal fluency

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INTRODUCTION

As the population ages, cultural diversity continues to change and grow at both a nationwide and global scale. Cultural diversity relates to both internal and external factors. Kitayama and Park (2010) explain that culture has three main constituents: explicit values, cultural tasks intended to achieve the culture's primary values, and the implicit psychological and neural tendencies aligning with those values. It is theorized that both micro (biological) and macro (behavioral) aspects of culture are associated with brain processes that change as a function of an individual's engagement in culture-specific ideas and practices, which supports the notion that there are dynamic

neuro-cultural interactions (Kitayama and Uskul, 2011). In other words, given that culture involves explicit behaviors and processes, synchronous firing of neurons during cultural tasks results in those neurons being wired together; therefore, cultural tasks can shape and modify neural pathways (Kitayama and Park, 2010).

In studying neuro-cultural interactions, the use of constructs such as race, ethnicity, nationality, and other related demographic variables have complicated research. Some argue that this type of categorizing lends itself to seeing culture-specific, "emic" (i.e., having to do with internal elements of a specific culture, ignoring cross-cultural schema) attributes as differentiating members of contrasting cultures, rather than using a more "pan-cultural" (i.e., having to do with culturally universal elements) approach (Bochner, 1994) that allows for the clustering of cultures based on an underlying process that spans categories used in past research (i.e., race, ethnicity, or nationality). Others have argued racial categories lack conceptual meaning when scientific method principles are applied (Helms et al., 2005). Specifically, racial categories are associated with a complex network of factors, such as biological (e.g., skin color) and social/socio-political factors (e.g., the experience of racism), that may limit interpretation of findings (e.g., why a racial group performs lower on cognitive tests than another). Most often, research that attempts to report or account for cultural diversity utilizes predetermined "check-box" classifications, such as race or ethnicity, where an individual is asked to check off a box that most closely describes how the person identifies him-/herself. Additionally, such labels create clear distinctions that do not account for individuals who effectively blur the lines between categories (e.g., individuals with dual-citizenship, persons who identify as being members of more than one group; Arnett, 2002). These methods of narrowly categorizing individuals may also impact statistical power to make inferences.

In light of the limitations of demographic variables like race/ethnicity, other cultural factors may provide added benefit when examining neuro-cultural interactions. One of the most basic cultural dimensions, how people perceive the self, has been central to how many culture-dependent differences are interpreted and explained. Described as construals of the self, or self-construals, that are either independent (or *individualistic*) or interdependent (or *collectivistic*), the development of self-perception can be traced to early childhood and parental rearing practices, then further reinforced by peers and society. Self-construals of individualism or collectivism (IC) have been implied as having possible consequences not only on social roles and interactions, but also on emotions, motivation, and cognition (Markus and Kitayama, 1991). Much of the research on self-construal and relevant cultural differences has relied primarily on an "East-West" paradigm. Western cultures (e.g., United States), described as highly individualistic, tend to place greater value on the personal self, applying a schema of independence to social perception, and grounding their emotional life and motivation primarily on personal goals, desires, and needs. Eastern cultures (e.g., Japan), described as highly collectivistic, place greater value on their interpersonal self, applying this schema to their social perception, and grounding their emotions and motivations largely on social goals and concerns (Kitayama and Park, 2010).

The individual development of cognition takes place in a cultural context. Self-construals may pull cognitive resources differently, and culture-dependent meaning systems may then alter neural processing (Chiao and Ambady, 2007). Studies examining IC-related group differences on functional magnetic resonance imaging (fMRI) have suggested differential cortical representation and functional distinctions in several frontal lobe regions, such as the medial prefrontal cortex (Chiao et al., 2010). This evidence supports the notion that self-construal is a higher order function potentially mediated by frontal networks. Of note, collectivism has recently been associated with a reduced orbitofrontal cortical volume (Kitayama et al., 2017), suggesting self-construal may interact with neuroanatomical changes in the frontal lobe that may be relevant to cognitive processes.

This role of culture on frontal lobe processes has been supported by cognitive research. There is evidence that collectivist children outperform individualists on various inhibition, card sorting, and tower-building tasks believed to be related to these higher order cortical processes (e.g., Sabbagh et al., 2006). In an adult sample, Cagigas (2008) reported evidence that cultural differences on cognitive measures may be more attributable to higher cortical functions than more primitive subcortical systems. Coupled with the evidence from neuroimaging research, an argument can be made that behavioral manifestations of frontal-lobe dependent cognitive processes exist between collectivists and individualists.

Developmentally, it is not clearly understood when in the lifespan particular cross-cultural cognitive differences begin to emerge (Kitayama and Uskul, 2011); as described above, differences are observed in young children. However, given gray and white matter changes that largely begin to occur later in life around middle age (Bartzokis, 2004), it is likely that the aging process further impacts cross-cultural differences in cognition. Although age-related changes in cognition have been extensively documented, little research has examined the impact of age in the context of self-construal and cognition. Aging represents the consequences of biological processes while culture represents sustaining experiences and their effects (Na et al., 2017). Age and self-construal may interact in a manner that impacts personal relevance and, therefore, cognition and processing of information. Indeed, citing other studies examining the activation of object-processing areas on fMRI and demonstrating age-by-culture interaction, it has been suggested that culture may modulate neurocognitive aging (Park and Gutchess, 2006). However, most evidence of cultural effects on neural function in the context of the aging brain has been in perceptual processing (Park and Huang, 2010).

In healthy aging, psychophysiological studies have shown a frontal phenomenon in cognitive processing. Age-related differences in frontal networks crucial for attention and executive functions (EFs) have been shown in brain imaging studies (e.g., McGinnis et al., 2011). While deterioration of

both gray matter and white matter are observed in healthy aging, some researchers now argue that cognition is associated more with white matter changes than with cortical thickness (Ziegler et al., 2010), and EF and processing abilities have been explained as the primary cognitive domain affected by white matter alterations (Murray et al., 2010). In light of the aforementioned implications of culture and higher cortical functions associated with the frontal lobe, age-related differences in frontal networks—both in gray and white matter—may interact with culture in a manner that impacts executive functioning abilities.

EFs are a multi-faceted construct generally understood as complex higher mental processes used in goal-setting, planning, and execution of plans (Lezak, 1982). One EF involves the production of intended actions while self-regulating through the inhibition of unrelated or irrelevant actions (Lezak et al., 2004), herein referred to as *cognitive fluency*. Neuropsychologically, cognitive fluency is often evaluated *via* measures where one is asked to rapidly generate a series of novel responses within a category or a set of rules and within a time limit (e.g., a minute).

Cognitive fluency tasks have been shown to be particularly sensitive to frontal lobe integrity (Baldo et al., 2001). This sensitivity may be due in part to the various components of fluency measures, such as semantic and inhibitory processes associated with cortical gray matter integrity (McDowd et al., 2011) as well as the speed of response and mental organization associated with white matter integrity (Kempler et al., 1998). Given the effects of aging on these areas, it is not surprising that performance on fluency measures is generally worse in older adults than in young adults (Elgamal et al., 2011).

The current study attempted to expand on the dearth of research by examining the relationship of IC with cognitive processes sensitive to frontal lobe functioning in an older population. As suggested by extant literature, self-construal may moderate age-related frontal lobe changes and, therefore, cognitive processes associated with frontal lobe integrity. Given the nature of collectivism and its prioritization of one's social group over the individual as well as the impact of aging on frontal lobe networks, we hypothesized that cognitive burden would be greater in this group. More specifically, we predicted that collectivism would be associated with greater demands on executive functioning and frontal lobe function, reducing the availability of frontally-mediated resources necessary to perform well on EF-dependent tasks. Therefore, it was expected that collectivists would perform lower than individualists on cognitive fluency measures. Additionally, it was expected that both groups would perform similarly on measures not related to cognitive fluency.

MATERIALS AND METHODS

Participants

Individuals at least 60 years old were recruited from the general community in San Diego, CA, USA using fliers and contacts with community programs serving older adults. Individuals who reported not feeling comfortable reading, writing, and speaking in English enough to complete study measures were excluded. Participants had to be community-dwelling adults able to provide written informed consent and not have endorsed a diagnosis of dementia or another cognitive disorder (e.g., mild cognitive impairment) at the time of testing. Although participants were not excluded from participation based on the history of psychiatric diagnoses or substance use, information regarding these factors was collected to control for their potential effect on performance in data analysis. Additionally, the Mini-Mental State Exam (MMSE; Folstein et al., 1975) was administered to participants to offer a brief screen for possible cognitive impairment associated with aging. Individuals with MMSE scores below 26 were not included in the data analysis. A total of 100 individuals were recruited. *A priori* standard power calculations indicated this sample size would be adequately powered to detect medium-to-large effects with an alpha level of 0.05.

All participants signed written informed consent approved by the Institutional Review Board at San Diego State University and were tested in person using paper-and-pencil versions of the measures described below. Testing was completed by a trained psychometrist in a quiet room, free of distraction, and took place either in a laboratory setting or in the community at a companion senior day center site. Testing lasted for approximately 1 h and participants received $10 for their participation.

Measures

Demographic

Participants were administered a semi-structured interview regarding their demographic background (e.g., birthplace, race and ethnicity, first language spoken, fluency in the English language, years living in the United States, acculturation) as well as pertinent medical history (e.g., history of head injury, learning disability, stroke, substance use). Validated self-report measures were used to assess bilingualism and acculturation. Given that the interview and test battery were administered in English, bilingualism and English-language dominance have implications on participants' responses and performance. Acculturation, while a construct dissociable and discrete from self-construal, may have implications on self-construal. An individual who is more acculturated to the dominant culture of where the individual resides may adopt values related to the self-construal typically observed within that culture (e.g., a person from a collectivistic culture, like Japan, who immigrates and acculturates to a "Western" culture, like the United States, may become more individualistic). For bilingualism, the Bilingualism Dominance Scale (BDS; Dunn and Fox Tree, 2009) was used. This brief scale is administered as an interview and consists of 12 items, which evaluate the person's predominant use of one language over another or the equal use of the two languages by targeting three main criteria: percent of language use, age of acquisition, and restructuring of language fluency. Original validation studies of the BDS showed it significantly predicted respondents' scores on objective measures of verbal fluency and translation reaction times. The Stephenson Multigroup Acculturation Scale (SMAS; Stephenson, 2000) was used to assess acculturation. This reliable and validated self-report measure of acculturation consists of

32 statements rated on a four-point scale (i.e., false, partly false, partly true, true). Items relate to domains of language, interaction, media, and food in the context of either the society of origin or the current society of residency. The measure allows for the calculation of two indices: the dominant society immersion (DSI) and the ethnic society immersion (ESI). Original validation studies of the SMAS showed high internal consistency for the entire scale (coefficient $\alpha = 0.86$) and for each of the indices (DSI = 0.97; ESI = 0.90).

Self-Construal

In a review of various survey methods, Peng et al. (1997) found significant limitations of rating and ranking measures in the assessment of self-construal when used to differentiate between cultures. Due to the unsatisfactory limitations of these methods, this study used a mixed methods approach using three measures validated for this purpose: INDCOL (Triandis, 1996), Scenarios (Triandis and Gelfand, 1998), and the Twenty Statements Test (TST; Kuhn and McPartland, 1954). Responses for the TST were coded by two raters blind to the participant's responses on other test materials, including other self-construal measures, and following the methods described elsewhere (Santamaría et al., 2010). Briefly, for purposes of determining self-construal, TST responses were coded along the domain of "organization" and statements were coded as either *private* (e.g., "I am smart"), *collective* (e.g., "I am a student"), or *public* (e.g., "I am someone who cares for others"). Raters were trained by the lead author on unrelated samples of TST responses that were not included in the current analyses. Once raters reached criterion (minimum Cronbach's alpha of 0.85), they began rating of TST responses from the recruited sample and were blind to participants' responses to the other measures of self-construal. Discrepant scores were regularly discussed with the lead author but were not removed from analyses. Inter-rater reliability was assessed using the intra-class correlation coefficient (ICC) and was found to be high (Cronbach's alpha = 0.97, ICC = 0.94).

Cognitive

The cognitive battery largely assessed for cognitive fluency as well as attention and working memory. Included in the battery were several tests. In the Action Fluency Test (Piatt et al., 1999), individuals name as many verbs as they can in a minute's time. Similarly, in phonemic letter fluency with FAS, respondents provide words that begin with the letters F, A, and S within a minute for each letter. In semantic fluency, responses are elicited for particular categories; animals and vegetables were used for the current study and each category was given a minute for responses. The Design Fluency subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) is a nonverbal measure in which respondents make line designs following specified rules within a minute. Attention and working memory abilities were assessed with the forward and backward conditions of Digit Span. These measures were chosen and categorized based on the neuroanatomical correlates they have been shown to represent. Verbal fluency measures like Action Fluency and FAS engage more left frontal lobe regions while semantic fluency (e.g., animals, vegetables), which relies more on conceptual knowledge, engages slightly more posterior regions (i.e., frontal-temporal areas) in the left hemisphere; in contrast, D-KEFS Design Fluency appears to engage right hemisphere frontal lobe regions in an analogous fashion to measures like FAS (Lezak et al., 2012). Measures of attention and working memory like Digit Span have shown evidence of broader, more diffuse engagement of brain regions; in addition to the bilateral involvement of dorsolateral prefrontal cortex, Digit Span performance appears to involve bilateral occipital and parietal areas that suggest use of visual imagery strategies during the task (Gerton et al., 2004). Reading ability in English was assessed with the Reading subtest of the Wide Range Achievement Test—Fourth Edition (WRAT-4; Wilkinson and Robertson, 2006). The WRAT-4 Reading has been shown useful in estimating premorbid ability and serving as a proxy of education quality in English, particularly in ethnically diverse samples with heterogeneous educational backgrounds (Manly et al., 2005).

Mood

Mood was assessed for each participant using the Geriatric Depression Scale (GDS; Yesavage et al., 1982), a validated measure of depression, to control for the possible effect of mood on cognition. Mood was then considered as a potential covariate and included in analyses as necessary.

Analysis

Self-Construal

Given the number of variables provided by the self-construal measures, latent profile analysis (LPA) was used to identify typologies of people, as opposed to a taxonomy of variables, along the lines of IC using the multiple variables provided by the self-construal measures. LPA is a person-centered technique in which an individual can be assigned to a mutually exclusive profile based on that individual's responses to observed continuous variables of interest by maximizing homogeneity within groups and maximizing heterogeneity between groups (Roesch et al., 2010). The process of LPA seeks to reveal the underlying latent construct of responses/scores (Lanza et al., 2003). Various models are tested to determine the optimal number of profiles and the best-fitting model is chosen based on various statistical indices of fit. IC measures provided a total of seven scores per participant that were included in the LPA. A 2-, 3-, and 4-profile solution were tested. By capitalizing on the shared variance of all the self-construal measures, LPA would allow for a more reliable, "error-free" (Roesch et al., 2010) categorization of individuals than would be achieved by using only a single measure.

Covariates

Relevant covariates were chosen for theoretical and statistical reasons. Covariates of interest included: ethnicity (Hispanic, non-Hispanic), race (White, non-White), age, gender, self-reported English fluency, WRAT-4, years in the United States, age when moved to the United States, bilingualism, acculturation, and mood (GDS). Univariable analyses were used to determine significant covariates. Cognitive domains were regressed on covariates of interest. Variables significant

at a $p \leq 0.10$ threshold were included as covariates in subsequent analyses.

Cognition

For data reduction purposes, composite scores were created such that cognitive measures of interest were grouped into four domains: Verbal Fluency (Action Fluency Test, FAS), Semantic Fluency (Animals, Vegetables), Nonverbal Fluency (Design Fluency Conditions 1 and 3), and Attention/Working Memory (Digit Span Forward and Backward). One-way analysis of covariance (ANCOVA) was used to examine the relationship of self-construal on cognitive domains. Data were checked for normality and outliers and missing data were excluded from analyses. Findings with *p*-values at or less than 0.05 were considered significant.

RESULTS

Of the 100 participants recruited, six individuals withdrew consent or were unable to complete all measures, seven were excluded from analyses due to MMSE scores less than 26, and one was excluded due to outlying values (>2 standard deviations) on several cognitive measures in addition to a history of head injury and self-reported cognitive symptoms. Therefore, 86 individuals (age: 67.2 ± 6.0; education: 14.5 ± 2.8) were included in the final analyses (**Table 1**).

LPA

Model fit indices for the LPA did not indicate a significant improvement of the 3- and 4-class solutions. Therefore, the more parsimonious 2-class solution was considered a better fit to the data (see Lubke and Muthén, 2005). Classification in LPA is based on the probabilities of being within a class/profile, which are related to the means of the individual indicators. A qualitative review of the 2-class solution (**Table 2**) revealed one profile (Class 1) consistent with higher scores on individualism scales compared to collectivism scales; therefore, Class 1 was labeled "individualists." Similarly, the profile observed in Class 2 was consistent with higher scores on collectivism scales relative to individualism scales and was labeled "collectivists" as a result. LPA results identified 42 individualists and 44 collectivists. Self-construal groups did not significantly differ on demographic variables, including gender, ethnicity, or race (**Table 1**).

Covariates

Univariable analyses with a $p \leq 0.10$ threshold determined inclusion of only four covariates: ethnicity, gender, GDS, and WRAT-4 Reading.

TABLE 1 | Sample demographics.

	Sample *N* = 86		Individualists *N* = 42		Collectivists *N* = 44		*p*
	Range	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	
Age (years)	60–88	67.2 (6.0)	60–88	66.9 (6.8)	60–78	67.6 (5.2)	0.600
Education (years)	8–20	14.5 (2.8)	8–20	15.0 (3.03)	8–20	14.0 (2.6)	0.100
Years in US	4–80	61.5 (14.5)	21–80	62.5 (10.7)	4–78	60.5 (17.5)	0.533
WRAT-IV	39–76	59.4 (7.9)	40–70	61.6 (6.8)	39–76	57.4 (8.5)	0.014
GDS	0–13	2.8 (3.2)	0–13	3.1 (3.7)	0–10	2.5 (2.7)	0.399
SMAS	−1.2 to 2.3	0.1 (0.5)	−0.6 to 2.3	0.2 (0.6)	−1.2 to 1.9	0.1 (0.5)	0.327
BDS—English	6–26	24.4 (4.1)	6–26	25.0 (3.7)	7–26	23.9 (4.5)	0.232
BDS—Other	−2 to 27	2.8 (6.3)	−2 to 27	1.7 (5.1)	−2 to 22	3.8 (7.1)	0.134
	n	**%**	***n***	**%**	***n***	**%**	***p***
Gender							
Male	40	46.5	22	52.4	18	40.9	0.387
Female	46	53.5	20	47.6	26	59.1	
Ethnicity							
Hispanic	6	7.0	2	4.8	4	9.1	0.677
Non-Hispanic	77	89.5	38	90.5	39	88.6	
Race							
American Indian	1	1.2	0	0	1	2.3	0.300
Asian	5	5.8	1	2.4	4	9.1	
African-American/Black	11	12.8	4	9.5	7	15.9	
Multiple	4	4.7	1	2.4	3	6.8	
Pacific Islander	1	1.2	0	0	1	2.3	
Unknown	3	3.5	1	2.4	2	4.5	
Caucasian/White	61	70.9	35	83.3	26	59.1	
Birthplace							
United States	74	86.0	38	90.5	36	81.8	0.213
Other	12	14.0	4	9.5	8	18.2	

Note: WRAT-IV, Wide Range Achievement Test—Fourth Edition, Reading Score; GDS, Geriatric Depression Scale (higher scores are associated with greater depressive symptoms); SMAS, Stephenson Multigroup Acculturation Scale (higher scores are associated with greater immersion in dominant society); BDS, Bilingual Dominance Scale (higher scores are associated with greater reliance on that language). "Other" birthplaces included Chile (1), Colombia (1), Iraq (1), Latvia (1), Philippines (4), Sweden (1), Switzerland (1), and Vietnam (1). For those born outside the US, self-reported years in the US ranged from 4 to 80 years (mean = 36.1 ± 22.1) and years speaking English ranged from 8 to 80 years (mean = 50.8 ± 18.8). Significance values were calculated using t-tests for Age, Education, Years in US, WRAT-IV, GDS, SMAS, and BDS; Fisher's exact test for Gender and Ethnicity; and Chi-square test for Race and Birthplace.

TABLE 2 | Means and standard deviations (SD) of self-construal measures.

Measure	Sample *N* = 86		Individualist *N* = 42		Collectivist *N* = 44	
	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)
IND	3.2–7.8	5.8 (1.1)	3.3–7.8	6.0 (1.1)	3.2–7.3	5.5 (1.1)
COL	3.1–9.0	6.8 (1.3)	3.1–8.5	6.2 (1.3)	5.1–9.0	7.3 (1.0)
Scenarios—Individualism	3.0–13.0	8.3 (2.4)	9.0–13.0	10.3 (1.4)	3.0–8.0	6.4 (1.5)
Scenarios—Collectivism	1.0–13.0	7.5 (2.5)	1.0–7.0	5.5 (1.5)	6.0–13.0	9.4 (1.5)
TST—Private	0.0–7.0	3.3 (2.2)	0.0–7.0	3.6 (2.2)	0.0–7.0	3.0 (2.1)
TST—Collective	0.0–7.0	2.4 (2.0)	0.0–7.0	2.1 (2.1)	0.0–6.5	2.7 (1.9)
TST—Public	0.0–4.0	0.9 (1.0)	0.0–4.0	0.9 (1.1)	0.0–4.0	0.9 (1.0)

Note: IND, INDCOL mean individualism score; COL, INDCOL mean collectivism score; TST, Twenty Statements Test.

Cognition

ANCOVA controlling for the determined covariates revealed a medium-sized main effect of self-construal on Verbal Fluency (Action Fluency Test, FAS), $F_{(1,77)} = 6.942$, $p = 0.010$, $\eta^2 = 0.061$. Comparing the estimated marginal means showed that collectivists ($M = 0.189$, SE = 0.113) outperformed individualists ($M = -0.252$, SE = 0.117). No significant differences (all $ps > 0.05$) were noted on Semantic Fluency (Animals, Vegetables), or Nonverbal Fluency (Design Fluency, both conditions). Both groups performed similarly (all $ps > 0.05$) on measures of Attention/Working Memory (Digit Span forward and backward; see **Figure 1**). The estimated means for individual tests included in composite scores are shown in **Table 3**.

DISCUSSION

In the current study, we examined the role of self-construal on frontal lobe-mediated processes. Given the cognitive demands associated with collectivism, which involves the consistent perception of self in the context of others, we hypothesized that collectivists would perform worse than individualists on measures of cognitive fluency. These measures were used as they are more focally sensitive to frontal lobe changes associated with the aging process. Along these lines, we expected both groups to perform similarly on non-fluency measures (i.e., attention/working memory as measured by Digit Span forward and backward), which rely on more diffuse brain regions. Contrary to our expectations, collectivists performed significantly better on measures of verbal fluency (phonemic, action) after controlling for ethnicity, gender, mood, and linguistic ability. Both groups performed similarly on semantic and nonverbal fluency as well as on tests of attention/working memory. These findings support previous literature suggesting that self-construal may be differentially associated with verbal and nonverbal measures (Hedden et al., 2002). Notably, race and ethnicity did not differ between groups, possibly highlighting the utility of measuring self-construal as an underlying perceptual process in cross-cultural research.

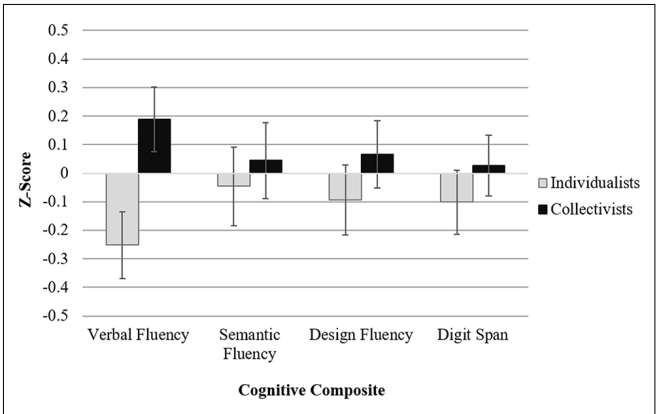

FIGURE 1 | Estimated means (SE) on cognitive measures by self-construal controlling for ethnicity, gender, Geriatric Depression Scale (GDS) score, and Wide Range Achievement Test (WRAT)-Reading score.

As described previously, verbal fluency measures rely on several processes linked to various cortical regions. Interestingly, performance on these measures does not always rely on semantic memory or vocabulary knowledge. McDowd et al. (2011) explain that overall performance on verbal fluency measures is most consistently predicted by the speed of processing with an additional, albeit secondary, contribution of executive processes. This synergistic effect of processing speed and executive functioning might explain why the effect was not found in untimed attention/working memory verbal tasks (Digit Span forward and backward) or in non-verbal design fluency, which relies primarily on motor planning and visual scanning rather than processing speed (Suchy et al., 2010). Future studies that include measures of processing speed are needed to further investigate this hypothesis.

Our results complement extant literature in various ways. These findings suggest a differential effect of IC on frontal lobe mediated cognition. In a young adult sample, our group previously reported no effect of self-construal on cognition in young adults (Medina et al., 2014). In light of the current results, an effect of age is suggested such that older collectivists may be more accustomed than individualists to such executive and processing demands and, thus, are more capable of compensating. Taken together with the results in young adults, it may be that normal cognitive decline as part of the aging process may magnify differences between collectivists and individualists. That is, aging may differentially impact individualists who may be less likely to compensate for executive declines as we observed in collectivists. Furthermore, our findings indicate that this cognitive advantage exists in verbal measures of both action and letter fluency, but is not evident in other measures of verbal and nonverbal fluency. While letter fluency also shares similar pathways with semantic fluency measures, it has been proposed

TABLE 3 | Estimated means (SE) on cognitive measures by self-construal controlling for ethnicity, race, and WRAT-Reading.

Measure	Individualist *N* = 42			Collectivist *N* = 44		
	Mean	SE	95% CI	Mean	SE	95% CI
AFT	21.94	0.83	20.3–23.6	23.12	0.80	21.5–24.7
FAS	32.03	1.72	28.6–35.4	37.78	1.66	34.5–41.1
Animals	18.01	0.71	16.6–19.4	18.94	0.68	17.6–20.3
Vegetables	11.54	0.60	10.4–12.7	12.15	0.58	11.0–13.3
Design fluency switch	6.03	0.25	5.3–6.7	6.19	0.33	5.5–6.9
Design fluency non-switching	8.59	0.45	7.7–9.5	9.00	0.43	8.1–9.9
DS-F	9.63	0.29	9.1–10.2	9.81	0.28	9.3–10.4
DS-B	6.62	0.30	6.0–7.2	6.68	0.29	6.1–7.3

Note: SE, standard error; CI, confidence interval; AFT, Action Fluency Test; FAS, phonemic fluency with F, A, and S; DS-F, digit span forward; DS-B, digit span backward.

that there is greater demand of initiation and maintenance of retrieval strategies in letter fluency, similar to action fluency, suggesting greater sensitivity to left frontal lobe function in letter fluency and action fluency than in tests of semantic fluency (Piatt et al., 1999).

The current findings additionally raise some questions regarding how self-construal can play a role in applied settings. For instance, demographic variables such as race and ethnicity are more commonly accounted for, or at least documented, in clinical settings and normative samples relative to IC. However, it is unknown how much of their effect on cognitive measures is potentially mediated or moderated by self-construal. Given the dynamic nature of culture, it is difficult to ascertain how these and other demographic variables interact to paint an individual's cognitive profile. More research in this area could help answer some of these questions.

This study was limited by several factors. The resulting sample size of 86 individuals was adequately powered (96%) for large effect sizes, but less powered (*post hoc* = 65%) for medium effect sizes. As shown in **Table 1**, the sample was limited in its diversity, particularly in relation to ethnicity and race, variables typically examined in the context of cultural differences and potentially related to self-construal. This might explain why, contrary to expectations, race and ethnicity were not related to self-construal. Nevertheless, while many studies on self-construal employ an East/West paradigm to capitalize on cultural differences, the study of self-construal within a homogeneous sample in a single culture has been previously demonstrated. For instance, work in this area has examined self-construal in both a purely Japanese sample, reflecting an "East," or collectivist, population (Kitayama et al., 2017), as well as in a purely United States sample, reflecting a "West," or individualist, population. Moreover, the self-construal scores observed in the reported sample are consistent with other published work on this topic. Specifically, on the TST, individualists showed a higher proportion of "private" or self-attribute (i.e., individualist) responses compared to collectivists, 72% vs. 22%, respectively—in a pattern consistent with results reported by Markus and Kitayama (1991); the opposite pattern was observed for collectivist responses on the TST: collectivists = 64%, individualists = 15%. Individualists and collectivists also demonstrated significantly different vertical individualism and vertical collectivism sub-scores in the expected directions on the INDCOL, consistent with the differences reported by Singelis et al. (1995) in a more diverse sample. Therefore, we are confident that the observed effect is consistent with the literature on self-construal. We hypothesize that this effect would be greater when using traditional East/West paradigms. In the context of our sample's limited ethno-racial diversity, our results further support the measure and study of self-construal as a variable separate from race and ethnicity.

The current study also had a limited cognitive battery. In spite of evidence that the measures administered are sensitive to cognitive decline in older adults (see Clark et al., 2012), it remains possible that not all these measures are sensitive enough to detect differences in a healthy sample of individualists and collectivists. A more expansive battery of tests that are more challenging or sensitive might aid future research. Cultural neuroscience research utilizing neuroimaging techniques such as EEG and fMRI has also elucidated how processes and brain activation patterns may differ between cultures while performance remains equivalent between groups (e.g., Kitayama and Park, 2010). Therefore, in a similar fashion, although individualists and collectivists may perform similarly on a cognitive task, differences in process may exist. Neuropsychological tests allowing for the measure of process approaches (e.g., serial clustering vs. semantic clustering in a verbal list-learning task, global vs. local attention to drawing sequence in a complex figure task) might aid in the identification of these.

Lastly, without true experimentation, it is not possible to posit any causality in the relationship between self-construal and cognition. Recent literature has demonstrated the benefits of being able to prime self-construal in individuals to investigate the impact of IC on psychological processes (Chiao et al., 2010) and that such priming can impact performance on a contextual memory task (Grossmann and Jowhari, 2017). The direct effect of IC could thus be examined in the context of cognitive fluency and other neuropsychological performance using a prime/no-prime experimental design.

Despite these limitations, these findings have implications for future research. Neuropsychological research methods typically focus on traditional demographics, primarily those including race, ethnicity, gender, and age. However, we still do not fully grasp the mechanism underlying the role of cultural variables in cognition (Manly, 2005). Likewise, we are limited in our understanding of how these interact with other cultural variables or how other variables are similarly related to cognitive processes. As has been proposed by Na et al. (2017), cognitive

functioning and cultural values may interact with each other through moderated mediation processes to determine cognitive processes. A cultural neuroscience framework incorporating multiple factors—micro and macro, biological and behavioral, process and performance—would aid greatly in expanding our comprehension of our increasingly diverse world. This attention to issues related to cultural diversity in our studies is likely to clarify past and future research findings.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Declaration of Helsinki and the American Psychological Association ethical standards with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the San Diego State University Institutional Review Board.

AUTHOR CONTRIBUTIONS

LM, MS, MY, JF, SW and PG all provided substantial contributions either to the conception and design of the study, analysis, and/or interpretation of the results. LM also participated in data acquisition (subject recruitment and cognitive evaluation). Additionally, all authors critically revisited the work, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

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frontiers in Human Neuroscience

BRIEF RESEARCH REPORT
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Age and Race-Related Differences in Sleep Discontinuity Linked to Associative Memory Performance and Its Neural Underpinnings

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There is a strong relationship between sleep and memory for the details of past events. In old age, both episodic memory performance and related neural activity decline. These changes occur in parallel to age-related decreases in sleep quality. Thus, poor sleep quality may be an explanatory factor for poor memory in older adulthood. Furthermore, Black adults tend to sleep more poorly than White adults, and this could be explained by differences in health and psychosocial factors (e.g., socioeconomic status, race-related stress). However, there have been no studies investigating the effect of race on sleep quality, episodic memory, and memory-related neural function. In the current pilot study, we recruited a diverse sample of older and younger adults and measured their habitual sleep using a wrist-worn accelerometer for 1 week. We recorded their electroencephalography (EEG) as they performed an episodic memory task to assess the impact of habitual sleep on memory-related neural oscillations. We found that more variable sleep quality was associated with worse memory performance, particularly for older adults. Additionally, Black participants demonstrated greater intraindividual sleep variance than White participants, and greater sleep variance was strongly linked to reduced memory-related neural activity in Black participants. Taken together, maintaining good sleep quality is especially important for memory performance in older adulthood, and greater sleep variation, that is evident in Black adults, may hamper memory-related neural function.

Keywords: sleep quality, episodic memory, neural oscillations, alpha, aging, diversity

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INTRODUCTION

The importance of sleep for memory consolidation has been firmly established (for a review, see Rasch and Born, 2013). Sleep manipulation studies (sleep vs. wake, sleep deprivation) show that episodic memory, or memory for previously experienced events, is sleep dependent in young and older adults (Yoo et al., 2007; Aly and Moscovitch, 2010; Payne et al., 2012; Wilson et al., 2012). Lab-based polysomnography studies have identified electroencephalography (EEG) sleep signatures that are indicative of memory consolidation (for a review see, Mander et al., 2017). It has been found that sleep spindles predict subsequent memory-related hippocampal activity in young and older adults (Mander et al., 2013). However, such studies do not allow for assessments of natural sleep patterns, from the comfort of one's own home, nor do they typically monitor sleep over multiple

nights. This type of measurement is necessary to examine habitual sleep quality, which has been tied to poorer memory in older adults (Wilckens et al., 2014; Cavuoto et al., 2016).

Meta-analyses and large studies have shown that older adults, as compared to young adults, are more likely to experience chronic sleep disruptions that include reduced total sleep time (TST) and increased wake after sleep onset (WASO; Carrier et al., 2001; Ohayon et al., 2004). There is also evidence that older adults experience more night-time awakenings (Dijk et al., 2001). Prior research suggests that older adults are not as affected by sleep as young adults are (Gui et al., 2017); however, these studies are typically limited to sleep-wake comparisons. Such broad manipulations do not capture individual differences in habitual sleep quality that may be more sensitive to memory in older adults. Importantly, individual differences in sleep quality measures, that can be captured by actigraphy, have been linked to individual differences in episodic memory performance, particularly in older adults (Mary et al., 2013; Wilckens et al., 2014; Seelye et al., 2015; Cavuoto et al., 2016). For example, research has shown that habitual sleep discontinuity, calculated as mean sleep disruption over time, (e.g., WASO) disproportionately affects memory recall in older adults (Wilckens et al., 2014). Subjective measures of sleep discontinuity have illustrated similar relationships; the self-reported number of night time awakenings has been negatively linked to associative memory recall in older, but not young adults (Mary et al., 2013). This limited evidence suggests that older adults are particularly sensitive to mean sleep discontinuity, but the relationship between night-to-night intraindividual variance in sleep discontinuity has not been studied.

While age-related differences in the effect of habitual sleep quality on episodic memory has been investigated, race-related differences in these effects are largely unexplored. The majority of research investigating age-related changes in sleep and memory has either not reported racial demographics of study participants or has been limited to predominantly White participant samples. Importantly, however, population studies have consistently reported poorer sleep in minorities, including Black and Latino Americans, than White individuals (Hicken et al., 2013; Slopen and Williams, 2014; Cunningham et al., 2016; Turner et al., 2016). Education has been related to sleep quantity and quality in minorities (Hicken et al., 2013; Slopen and Williams, 2014; Turner et al., 2016), but this relationship is thought to be confounded by variables associated with lower education such as poorer living and working conditions (Bixler, 2009). Moreover, a few studies have shown that after adjusting for education, psychosocial factors, particularly discrimination and race-related stress, explain racial/ethnic differences in sleep quality (Hicken et al., 2013; Slopen and Williams, 2014). However, it is important to note that these studies subjectively measured sleep quality with short questionnaires. Thus, it remains unknown if similar racial differences exist for objectively measured sleep quality and the extent to which such differences contribute to individual differences in memory performance.

The underlying neural oscillations involved in episodic memory have not been explored in relation to habitual sleep quality. Neural oscillations in the alpha and theta frequency have been consistently linked to memory performance (for a review see, Hanslmayr et al., 2012; Hanslmayr et al., 2016). One such study found that alpha desynchronization increases as a function of the amount of successfully retrieved information (Khader and Rösler, 2011). Furthermore, compared to restful sleep, acute sleep restriction has been shown to reduce retrieval-related alpha desynchronization (Alberca-Reina et al., 2015). Thus, the research demonstrates that sleep is related to waking, memory-related neural activity. However, there is an absence of research examining these effects in relation to habitual sleep quality, or sleep over time, which emphasizes the necessity of the present pilot study.

The current study is the first to examine interactions between age and race on both the mean and intraindividual variance of habitual sleep quality and their contribution to episodic memory performance and related neural activity. Given evidence showing that sleep affects memory performance and memory-related neural activity during episodic retrieval (for a review see, Kreutzmann et al., 2015), we hypothesize that poorer and more variable habitual sleep quality will predict worse memory performance and reduced memory-related neural oscillations. Furthermore, considering the well-established reductions in sleep quality in older adults and minority groups, poor sleep quality may disproportionately relate to memory performance in older, Black participants.

MATERIALS AND METHODS

Participants

Eighty-one participants (45 older, 36 younger) from the Georgia Institute of Technology and the Atlanta community enrolled for the present study. Young adults were recruited within the age range of 18 to 37 years, and older adults were recruited from 56 to 76 years. All participants were right-handed, native English speakers, with normal or corrected to normal vision, free of uncontrolled psychiatric disorders, neurological disorders, sleep disorders, and vascular disease. All participants signed consent forms approved by the Georgia Institute of Technology Institutional Review Board.

Sleep data for all 81 participants were used for a principal components analysis (PCA) of sleep data (see section "Principal Components Analysis"). Eleven of the 81 subjects were excluded from further analyses because they were run on an early procedure in which a delay was placed between encoding and retrieval, 2 did not finish the experiment, 7 had insufficient numbers of trials for EEG analysis (i.e., fewer than 10 misses or high confidence hits), and 11 did not identify as either Black or White. The age and racial breakdown of the final sample are shown in **Table 1**.

Procedure

Participants were administered a battery of standardized neuropsychological tests to rule out mild cognitive impairments. The test battery consisted of subtests from the Memory Assessment Scale (Williams, 1991) including list recognition, visual recognition, and verbal span. Participants also

TABLE 1 | Group characteristics by age and race.

Measure	Young		Old				
	Black (n = 11)	White (n = 9)	Black (n = 9)	White (n = 21)	1	2	3
Age	25.09 (1.71)	22.89 (1.36)	63.33 (1.65)	69.42 (0.97)	**	***	
Gender (Women/Men)	6/5	6/3	4/5	12/9			
Education	15.00 (0.38)	15.44 (2.79)	15.22 (0.70)	15.29 (0.46)			
High Confidence *d'*	1.69 (0.20)	1.65 (0.77)	1.33 (0.23)	1.04 (0.17)		*	
High Confidence Trials	0.67 (0.05)	0.64 (0.03)	0.73 (0.05)	0.75 (0.04)			
List Recognition	11.75 (0.16)	12.00 (0.00)	11.50 (0.27)	12.00 (0.00)			*
Visual Recognition	16.82 (1.27)	17.67 (1.27)	13.11 (1.86)	15.43 (0.92)		*	
Verbal Span	12.64 (0.62)	11.33 (1.00)	9.22 (0.74)	10.95 (0.55)		*	
Trials A (seconds)	25.62 (2.51)	22.85 (1.92)	35.19 (3.00)	35.63 (2.71)		*	
Trials B (seconds)	66.91 (9.77)	54.45 (5.86)	101.50 (13.01)	67.67 (2.85)		*	*
MOCA	27.55 (0.37)	28.00 (0.55)	23.33 (1.01)	27.40 (0.41)	***	***	**
DASS-Stress	3.00 (1.12)	4.78 (1.28)	2.78 (0.98)	3.52 (0.71)			
IRRS-B Cultural	28.75 (5.12)	21.25 (3.12)	28.00 (7.08)	14.33 (2.20)			**
IRRS-B Institutional	10.50 (2.40)	9.75 (2.17)	12.25 (3.54)	6.50 (0.50)			*
IRRS-B Individual	11.25 (3.35)	7.50 (1.50)	13.33 (2.40)	6.44 (0.44)			*
Income			33434.67 (4851.62)	59856.71 (4013.46)	**		
TST-M	397.93 (20.32)	417.89 (17.92)	350.95 (15.04)	411.37 (11.39)			*
TST-V	12706.23 (4561.47)	5047.56 (1200.78)	5046.26 (1552.16)	3889.18 (978.34)			*
Number of Awakenings-M	15.70 (2.15)	16.16 (2.42)	17.96 (2.71)	13.23 (0.97)			
Number of Awakenings-V	43.31 (9.00)	23.70 (4.40)	25.28 (6.22)	20.20 (4.20)			
Sleep Efficiency-M	87.27 (1.51)	88.65 (2.84)	82.55 (3.90)	89.64 (0.90)			*
Sleep Efficiency-V	29.94 (8.41)	25.71 (16.22)	34.22 (15.88)	21.01 (4.24)			
WASO-M	49.14 (6.43)	47.53 (13.84)	74.17 (19.49)	43.80 (4.48)			
WASO-V	841.74 (290.19)	557.76 (367.69)	596.88 (139.94)	660.88 (181.70)			
SFI-M	29.48 (3.01)	24.03 (4.03)	40.26 (5.16)	24.67 (1.25)			**
SFI-V	134.31 (31.57)	90.43 (18.42)	169.09 (33.03)	114.24 (18.28)			
Sleep Discontinuity Component - M	0.06 (0.28)	−0.03 (0.34)	0.57 (0.51)	−0.26 (0.13)			
Sleep Time Component- M	0.05 (0.31)	0.47 (0.34)	−0.63 (0.22)	0.23 (0.17)		*	
Sleep Discontinuity Component-V	0.39 (0.35)	−0.20 (0.25)	−0.32 (0.22)	−0.30 (0.22)			
Sleep Time Component - V	0.32 (0.46)	−0.33 (0.21)	0.35 (0.43)	−0.14 (0.17)			

*The standard error of the mean is in parentheses. Mean differences between old Black and old White are in column 1; age group main effects are marked in column 2; and racial group main effects are in column 3. There were no significant differences between young Black and young White participants. The IRRS-B measures are based on a smaller subset of participants. TST = Total Sleep Time; WASO = Wake After Sleep Onset; SFI = sleep fragmentation index; M = mean; V = variance. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

completed Trials A and B, a subtest of the Halstead-Reitan Neuropsychological Test Battery (Reitan and Wolfson, 1985). Lastly, the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005) was administered to further test for mild cognitive impairments. The MOCA cutoff score of 26 was used as a guide in conjunction with the other neuropsychological tests, as the MOCA was developed in Montreal and may not be able to fairly assess the cognitive status of people from different educational, cultural, and racial backgrounds (Manly, 2005; Sink et al., 2015; Carson et al., 2017). Given that the aim of this study was to investigate a diverse sample, we did not exclude participants who scored lower than 26 on the MOCA. Instead, we examined scores from both the neuropsychological assessment and experimental task to ensure that the participants could perform the tasks and did not suffer from cognitive impairment.

On the first lab visit, participants were given an accelerometer and an activity log. They were instructed to wear the ActiGraph wGT3X-BT accelerometer at all times (except for situations where water may damage the device such as when bathing or swimming).

They returned to the lab after a week of sleep measurement, and EEG was recorded as they performed an associative memory task (see **Figure 1**). Word stimuli for the memory task was chosen using two methods. In the first method, words were generated from the MRC Psycholinguistic Database: Machine Usable Dictionary, Version 2.00 (Wilson, 1988) according to general standards from previous studies (Dockree et al., 2015). All words ranged from 4 to 6 letters with a written frequency of 2 to 60. They had concrete and imaginability ratings of 300 to 700 (Frances and Kucera, 1982). We compiled 45 word pairs using this method and classified them into low, medium, and high similarity levels. For the second method, 207 word pairs were collected from a combination of databases that had empirically based similarity ratings (Finkelstein et al., 2002; Li et al., 2013;

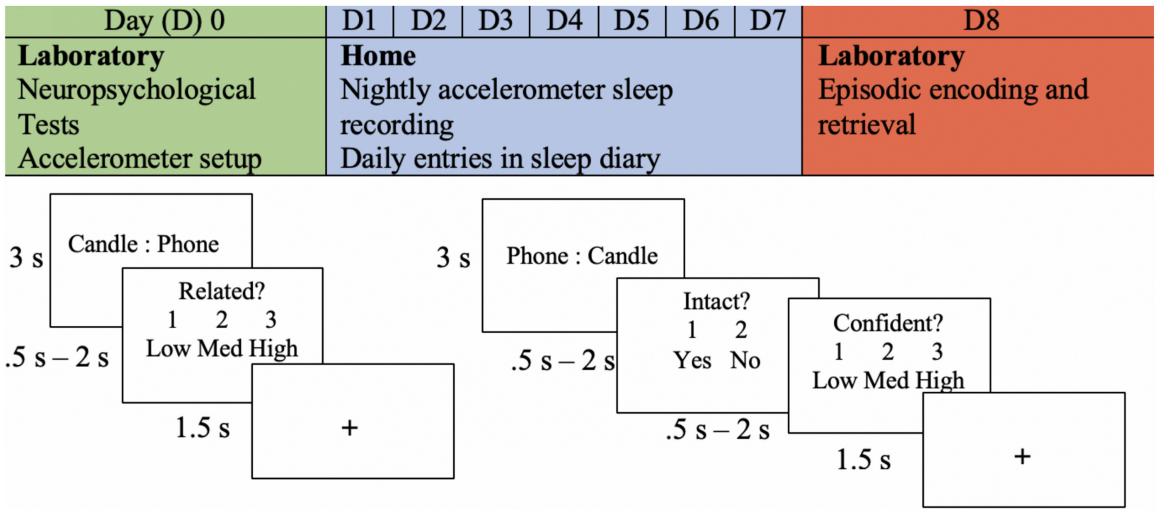

FIGURE 1 | Experimental procedure. An example of the experimental procedure and the memory task is shown. The encoding task is shown in the bottom left, and retrieval is shown in the bottom right. The depicted trial is an example of an intact pairing.

Szumlanski et al., 2013; Hill et al., 2015). The word pairs were divided into separate categories for low, medium, and high similarity. Similarity levels were counterbalanced across blocks of the encoding task.

Encoding was divided into four blocks. Each block consisted of 63 trials, and each trial began with a word pair that remained on the screen for 3 s. On the following screen, participants were prompted to determine the similarity between the word pair previously presented. This task was given to encourage deep encoding and to minimize the use of varying mnemonic strategies across participants. They were given the options of "1" for minimally related to "3" for highly related (indicated as low, medium, and high). Participants had a minimum of 0.5 s and a maximum of 2 s to make this decision. In other words, if a response was given before 0.5 s, the trial ended at 0.5 s; if a response was given after 0.5 s, the trial ended at that time. This method was chosen to allow participants who were slower enough time to respond, while also accommodating those who responded faster.

Participants began the intact/rearranged retrieval task shortly after encoding. Intact word pairs were presented with the same word that they were presented with at encoding, but the words in the first position were changed to the second position to avoid unitization of the word pairs (see **Figure 1**). Rearranged word pairs were presented with different words than paired with during the encoding task. No new words were presented at retrieval. One-third of the word pairs presented during encoding were rearranged, and two-thirds remained intact. This method was chosen to maximize the potential for data analysis, as only responses to intact word pairs were able to be compared to those during encoding. The task was divided into four blocks, each consisting of 63 trials. Each trial included an intact/rearranged decision and confidence judgement; participants were prompted to indicate their confidence in their response (low, medium, or high). The minimum time allotted for both responses was 0.5 s and the maximum was 2 s. There were three versions of the retrieval task that were counterbalanced across participants. Given that two-thirds of the pairs were intact and one-third of the pairs were rearranged, the third of the pairs that were rearranged were modified in each version. Thus, each pair was in the rearranged set in one of the versions.

After completion of the study participants were given a set of questionnaires to assess mood, caffeine intake, subjective sleep quality, and preferred time of day: the Pittsburg Sleep Quality Index (Buysse et al., 1989), Epworth Sleepiness Scale (Johns, 1991), the 21-item version of Depression, Anxiety, and Stress Scale (DASS-21; Lovibond and Lovibond, 1995), the Caffeine Intake Questionnaire (Landrum, 1992), and the Morningness Eveningness Questionnaire (Horne and Ostberg, 1976). Participants were later emailed an online questionnaire to assess experiences of race-related stress using the Index of Race-Related Stress-Brief (IRRS-B; Utsey and Ponterotto, 1996).

EEG Acquisition

Electrophysiological signals were recorded from 32 Ag-AgCl electrodes using an ActiveTwo amplifier system (Biosemi, Amsterdam, Netherlands). Electrodes were positioned according to the extended 10–20 system (Nuwer et al., 1998). Electrodes were located at left/right hemisphere locations (FP1/FP2, AF3/AF4, F3/F4, F7/F8, FC1/FC2, FC5/FC6, C3/C4, T7/T8, CP1/CP2, CP5/CP6, P3/P4, P7/P8, PO3/PO4, O1/O2) and midline sites (Fz, Cz, Pz, Oz). Two electrodes were placed on the left and right mastoids for offline referencing. Vertical electrooculogram and horizontal electrooculogram were monitored by four additional electrodes placed above and below the right eye and on the outer canthus of each eye, respectively. The ActiveTwo system replaces traditional reference and ground electrodes with common mode sense and driven right leg electrodes, respectively. EEG was acquired with 24-bit resolution at a sampling rate of 512 Hz.

EEG Analysis

Offline EEG preprocessing was performed using EEGLAB (Delorme and Makeig, 2004), ERPLAB (Lopez-Calderon and Luck, 2014), and FIELDTRIP (Oostenveld et al., 2011) toolboxes, and this process was based on previous research in our lab (see Strunk et al., 2017). Continuous data was resampled to 256 Hz, referenced to the average value of the left and right mastoids, and band-pass filtered between 0.5 and 125 Hz. The data was epoched to the stimulus presentation (i.e., appearance of word pair at 0 ms) from −1000 to 3500 ms. Then, independent components analysis was run for ocular artifact detection. The independent components analysis was run on the first 20 principle components of the head electrodes. Components that resembled ocular artifacts (e.g., eye blinks and horizontal eye movements) were manually removed. Then, an automatic rejection algorithm was applied in order to detect extreme voltage shifts across more than one electrode. Following this process, the data was visually inspected to assess the epochs selected for rejection, and any ocular, electrical, or muscle artifacts were manually removed. The frequency decomposition was performed using Morlet wavelets with linearly spaced frequencies between 2 and 40 Hz at 5 cycles. The frequencies of interests were defined as theta (4 to 7 Hz), alpha (8 to 12 Hz), and beta (16 to 26 Hz).

Actigraphy Data

The sleep variables of interest were the means and variances (calculated as the squared standard deviation across each participant's week of sleep) for TST, WASO, sleep fragmentation index (SFI), and number of awakenings. TST is the total minutes spent asleep, and WASO is the sum of minutes spent awake after initially falling asleep. The SFI is a measure of restlessness during sleep; the number of awakenings is the frequency of awakenings during sleep.

Statistical Analysis

The statistical analyses were conducted using the Statistical Package of Social Sciences 24 (SPSS). In an effort to measure recollection-based memory, which is disproportionately affected by age and sleep (Drosopoulos et al., 2005; Koen and Yonelinas, 2014), memory performance was limited to *d'*, calculated as the standardized proportion of high confidence hits subtracted from the standardized proportion high confidence false alarms. High confidence memory decisions have been found to be sensitive to age-related differences (Shing et al., 2009; Fandakova et al., 2013).

We used analysis of variance (ANOVA) to determine age and racial group differences. Age and racial group were entered as independent variables, and the dependent variables, neuropsychological measures, sleep discontinuity (mean and variance), and *d'*, were separately assessed. Lastly, relationships between measures of sleep discontinuity, and dependent variables, *d'* and memory-related neural oscillations were examined. The PROCESS macro (Hayes, 2018) was used to determine if the relationships between sleep and memory were moderated by age group (young or old) or racial group (Black or White).

RESULTS

One older participant was not administered the MOCA because of having recently taken it. No participants were excluded for low MOCA scores, as all participants in the final sample were able to perform the experimental task, and the MOCA score did not reliably predict *d'* performance [$r(47) = 0.034$, $p = 0.815$]. Thus, we retained the final sample of 50 participants (20 young, 30 old).

Principal Components Analysis

Because of the intercorrelations among the sleep variables, we used PCA with Varimax rotation to obtain discrete sleep components. We included all enrolled participants (81; 36 young, 45 older) to obtain reliable components. We ran separate PCAs for the means and variances of the sleep variables. PCA components were retained if the Eigenvalues exceeded 1. Each PCA resulted in two components for the sleep means and sleep variances. Components were extracted as regression variables to examine their relationships with memory and underlying neural oscillations. Since the components were largely representations of disturbed sleep and sleep time or general fragmentation, we will refer to the first component as sleep discontinuity and the second as sleep time (see **Table 2**).

Alpha Desynchronization Memory Success Effect

We assessed mean differences for the contrast between high confidence hits and misses using cluster-corrected permutations (Oostenveld et al., 2011). Memory success effects were not found in the theta or beta frequency band. There were significant mean differences across participants in the alpha frequency from 440 to 1360 ms [$t(49) = -4.691$, $p = 0.001$]. The effect extended over 28 electrodes. Considering the broad topography of this effect, we divided the electrodes into frontal (Fp1;Fp2;AF3;F3;FC1;FC2;FC5;FC6;Fz), central (T7;T8;C3;C4;CP1;CP2;CP5;CP6;Cz), and posterior (P7;P8;P3;P4;PO3;PO4;Pz;O1;O2;Oz) regions to allow for the assessment of distinct spatial regions related to episodic memory;

TABLE 2 | Sleep variable loadings for principal component analysis.

	Sleep Variable	Sleep Discontinuity	Sleep Time
Mean	Total Sleep Time	–0.078	**0.974**
	Wake After Sleep Onset	**0.919**	–0.203
	Sleep Fragmentation	**0.825**	–0.420
	Number of Awakenings	**0.909**	0.159
Variance	Total Sleep Time	**0.523**	0.504
	Wake After Sleep Onset	**0.736**	0.091
	Sleep Fragmentation	–0.022	**0.943**
	Number of Awakenings	**0.898**	–0.011

The table displays the loadings for the sleep variables of interest. Bold text indicates the dominant variables.

these contrasts were all statistically significant ($p \leq 0.002$). Each participant's mean for these memory success effects (high confidence hit vs. miss) were used to examine correlations between *d'* and sleep discontinuity.

Age and Racial Group Differences in Memory and Sleep Quality

An Age Group (Young, Old) × Race (Black, White) ANOVA revealed a main effect of Age for *d'* [$F(1,46) = 5.96$, $p = 0.033$, $\eta^2 partial = 0.095$]. There was no significant main effect of Race or interaction effect ($p > 0.47$). In the present sample, only the mean sleep time component demonstrated a significant main effect of Race ($p = 0.02$, $\eta^2 partial = 0.115$; see **Table 1**); however, all sleep components in the behavioral sample reached significant main effects of Race ($p < 0.03$), indicating worse sleep quality in Black participants. Thus, we examined each sleep component as an independent variable of interest for the following correlational analyses.

Association Between Habitual Sleep Discontinuity and Memory Performance

After controlling for chronological age, sleep discontinuity variance correlated with *d'* in older adults [$r(26) = -0.462$, $p = 0.013$], but not young [$r(16) = 0.168$, $p = 0.505$]. Age group significantly moderated this relationship, even after controlling for years of age [$\Delta R^2 = 0.09$, $F(1, 43) = 5.30$, $p = 0.03$; see **Figure 2A**]. No other moderation effects between the sleep components and *d'* reached statistical significance.

Association Between Habitual Sleep Discontinuity and Alpha Desynchronization

After controlling for chronological age, sleep discontinuity variance significantly correlated with reduced memory-related alpha desynchronization for Black [$r(15) = 0.685$, $p = 0.002$, but not White $r(27) = 0.007$, $p = 0.969$] participants, particularly in posterior electrodes (see **Figure 2B**). Race significantly moderated this relationship after controlling for chronological age [$\Delta R^2 = 0.12$, $F(1, 43) = 6.75$, $p = 0.013$]. No other moderation effects between alpha desynchronization and the sleep components were statistically significant.

Age and Race-Related Differences in Moderation Effects

Taken together, the results demonstrate that intraindividual variance in habitual sleep discontinuity is linked to memory performance in older adults and memory-related alpha desynchronization in Black adults. A conceptual model of these findings is depicted in **Figure 2C**.

Race-Related Stress

The racial relationships found above could be related to differences in socioeconomic status. Based on zip code census data, Black participants reported living in poorer areas than White participants [$t(28) = -3.381$, $p = 0.001$]. This analysis was limited to the older adult sample because the young adults were Georgia Tech students with similar zip codes. An Age Group (Young, Old) × Race (Black, White) ANOVA for the IRRS-B subscales demonstrated that Black participants, across age, reported more cultural, institutional, and individual experiences of race-related stress [$F(1,16) = 10.09$, $p = 0.006$, $\eta^2 partial = 0.387$; $F(1,16) = 5.23$, $p = 0.035$, $\eta^2 partial = 0.249$; $F(1,15) = 8.33$, $p = 0.011$, $\eta^2 partial = 0.357$]. Furthermore, variance in SFI was positively related to both cultural and individual race-related stress after controlling for chronological age [$r(15) = 0.522$; $r(15) = 0.498$, $p < 0.05$]. There were no racial group differences in the general stress variable measured by the DASS [$F(1,46) = 1.51$, $p = 0.226$, $\eta^2 partial = 0.032$].

DISCUSSION

The results of the present study reveal interesting interactions among variance in sleep discontinuity, associative memory, aging, and race. Consistent with previous research (Hicken et al., 2013; Slopen and Williams, 2014; Cunningham et al., 2016; Turner et al., 2016), we found numerical differences across measures of sleep discontinuity, illustrating that Black adults maintained poorer sleep quality than White adults. Differing from prior studies, we investigated the effects of the variance in sleep quality, or the changes in night-to-night sleep stability, on memory. We found that greater variance in sleep quality predicted worse memory performance in older adults, but not young. Sleep variance was also associated with reductions in the memory success effect of alpha desynchronization in Black adults, but not White adults, across age. In addition, neuropsychological measures of cognitive performance (e.g., MOCA) were not reliable predictors of high confidence memory performance, but sleep discontinuity was a reliable predictor. This result supports the notion that excluding participants using such measures may unnecessarily reduce racial/ethnic diversity in cognitively normal samples (Sink et al., 2015; Carson et al., 2017). These novel findings suggest that maintaining good sleep quality is especially important for memory in older adults and Black adults.

Older adults may be more sensitive to sleep quality because of age-related neuropathology such that age-related neural changes and poor sleep act as an additive effect to reduce memory performance (for a review see, Scullin, 2017). Moreover, race may moderate the relationship between sleep discontinuity and memory-related alpha desynchronization not inherently because of race, but because of race-related psychosocial factors. For example, we found that older, Black participants reported living in poorer areas, and Black adults across age reported experiencing more race-related stress. Moreover, stress levels have been found to affect confidence in memory, which could be related to a greater reliance on familiarity than recollection (Corbett et al., 2017). Greater sleep discontinuity in Black adults could be explained by interactions between stressful experiences of discrimination and health problems (e.g., greater body weight, diabetes, and heart disease) that commonly affect minority groups (Karlsen and Nazroo, 2002; Williams et al., 2015). Consistent with our findings, meta-analysis results show that

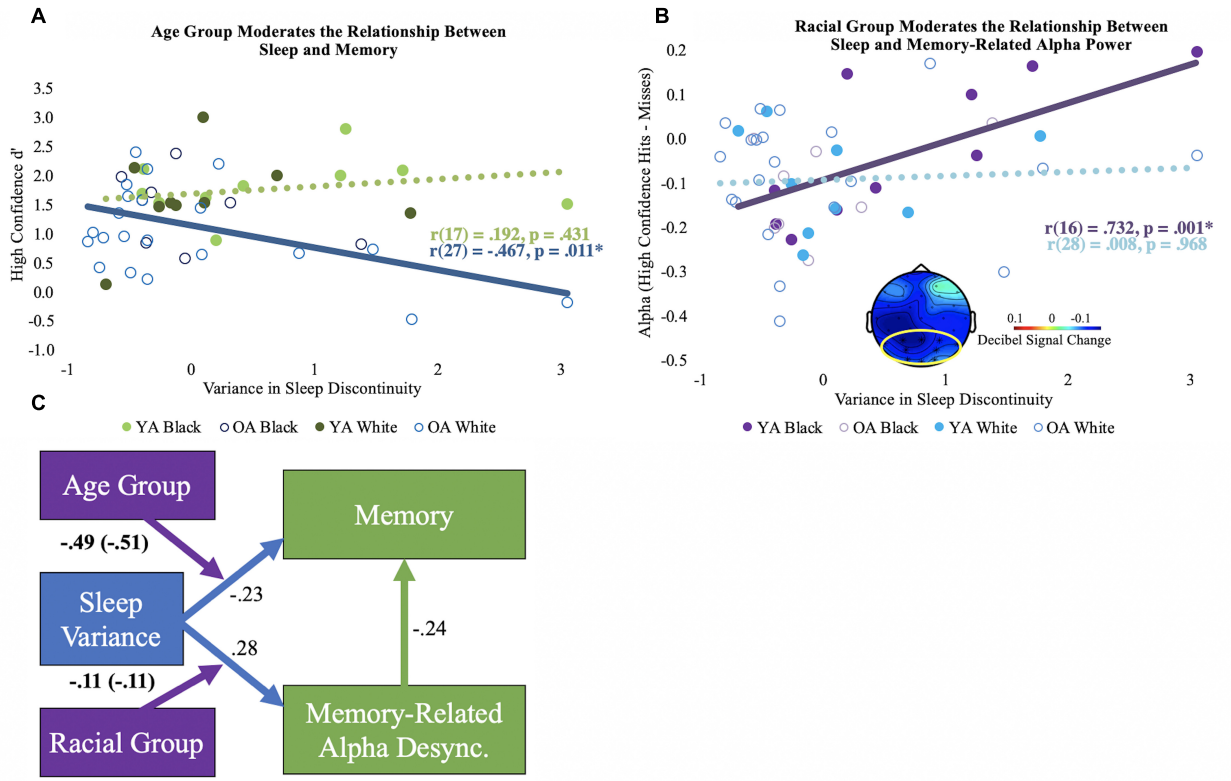

FIGURE 2 | Moderation results. **(A)** Bivariate correlations (unadjusted) for the variance in sleep discontinuity and high confidence *d'* by age group. The significant correlation is shown using a solid line, and the non-significant correlation is shown using a dotted line. **(B)** Bivariate correlations (unadjusted) for the variance in sleep discontinuity and alpha desynchronization (high confidence hits minus misses) by racial group. The mean alpha desynchronization effect in the posterior electrode cluster (outlined in yellow; 440 to 1360 ms) is shown in bottom center of the plot. Each participant's alpha power mean is shown. Significance is illustrated the same as in panel **(A)**. **(C)** Conceptual model of the moderation results. The direct paths for sleep discontinuity are shown in blue. The direct path for the correlation coefficient for memory-related alpha desynchronization and memory performance is depicted in green. Direct paths reflect the correlations across age and racial groups and are adjusted for chronological age. The moderator variables are shown in purple, and the age-adjusted interaction coefficients are displayed. Interaction coefficients that are not adjusted for age are in parentheses. Boldface indicates significant statistics. Desync = desynchronization.

more variance in sleep quality is often found in minority groups and young adults, and it is often associated with poor physical and psychological health (Bei et al., 2016).

Nonetheless, research for night-to-night variance in sleep quality is particularly scarce, and the studies that have examined sleep variance are often limited to subjective, self-report measures (Bei et al., 2016). It should be noted that there are often discrepancies between self-report sleep measures and objective sleep measures, especially for night-time awakenings (King et al., 2017). Furthermore, relationships between natural sleep patterns and the neural underpinnings of memory are largely unknown. Most of the sleep and memory research is focused on sleep manipulations instead of habitual sleep quality, and there are no studies (to our knowledge) that investigate interactions between objective sleep quality, age, and race in relation to memory performance. Given that both minorities and older adults tend to sleep more poorly than other populations, it is surprising that these relationships have not been investigated. Future research should include race as a variable of interest in their studies, considering that the present study found that Black adults had poorer sleep and a relationship between sleep and memory-related neural activity.

This pilot study is limited by its small sample size. It is also limited by its cross-sectional nature; thus, we cannot determine a causal relationship among the examined factors.

Although sleep difficulties are often found in older adults and minorities (Ohayon et al., 2004; Bei et al., 2016), the memory-related neural consequences of these effects are poorly understood. The results of this study highlight the importance of objectively investigating habitual sleep quality in larger, more diverse samples.

CONTRIBUTION TO THE FIELD STATEMENT

At least one in every three adults regularly obtains insufficient amounts of sleep, and those who do not maintain good sleep quality are disproportionately older adults, racial/ethnic minorities, or both older and of minority status. However, very little is known about the neurocognitive consequences of

poor, objectively measured habitual sleep quality, specifically its effect on episodic memory. No prior study has investigated this relationship with both age and race as variables of interest. The current study found that older adults may be more sensitive to sleep discontinuity, as their memory performance was worse when there was greater variance in measures of sleep disruption. Furthermore, Black adults slept more poorly than White adults, and they demonstrated a relationship with memory-related neural oscillations and sleep discontinuity such that greater night-to-night variance in sleep discontinuity weakened memory-related neural activity. Thus, the results from the current study suggest that poor habitual sleep quality may have differential effects on memory depending upon age and racial group. These findings highlight the necessity of further investigating the relationship between habitual sleep quality and episodic memory in diverse samples.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Central Institutional Review Board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the IRB. The protocol was approved by the Georgia Tech IRB.

AUTHOR CONTRIBUTIONS

EH contributed to the conceptual design of the study and collected and analyzed the data. AD guided the conceptualization of the study and the interpretation of the results. EH and AD wrote the manuscript.

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Disparities in Diffuse Cortical White Matter Integrity Between Socioeconomic Groups

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There is a growing literature demonstrating a link between lower socioeconomic status (SES) and poorer neuroanatomical health, such as smaller total and regional gray and white matter volumes, as well as greater white matter lesion volumes. Little is known, however, about the relation between SES and white matter integrity. Here we examined the relation between SES and white matter integrity of the brain's primary cortical regions, and evaluated potential moderating influences of age and self-identified race. Participants were 192 neurologically intact, community-dwelling African American and White adults (mean age = 52 years; 44% male, 60% White, low SES = 52%) from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) SCAN study. Participants underwent 3.0-T cranial magnetic resonance imaging. Diffusion tensor imaging was used to estimate regional fractional anisotropy (FA) to quantify the brain's white matter integrity and trace to capture diffusivity. Multiple regression analyses examined independent and interactive associations of SES, age, and race with FA of the frontal, temporal, parietal, and occipital lobes bilaterally. Sensitivity analyses assessed the influence of several biopsychosocial risk factors on these associations. Exploratory analyses examined these relations with trace and using additional SES indicators. Results indicated there were no significant interactions of SES, age, and race for any region. Individuals with low SES had lower FA in all regions, and higher trace in the right and left frontal, right and left temporal, and left occipital lobes. Findings remained largely unchanged after inclusion of sensitivity variables. Older age was associated with lower FA and greater trace for all regions, except for the right temporal lobe with FA. No main effects were found for race in FA, and Whites had higher trace values in the parietal lobes. Novel findings of this study indicate that relative to the high SES group, low SES

was associated with poorer white matter integrity and greater diffusivity. These results may, in part, reflect exposures to various biopsychosocial risk factors experienced by those of lower SES across the lifespan, and may help explain the preponderance of cognitive and functional disparities between socioeconomic groups.

Keywords: white matter integrity, health disparities, diffusion tensor imaging, socioeconomic status, race, age, neuroanatomical health

INTRODUCTION

There is a burgeoning literature demonstrating a link between socioeconomic status (SES) and neuroanatomical health. For instance, on average, those lower on the socioeconomic ladder have smaller total (Waldstein et al., 2017) and regional gray and white matter volumes (for reviews see: Hackman and Farah, 2009; McEwen and Gianaros, 2010; Brito and Noble, 2014). Studies have also shown that lower childhood (Murray et al., 2014) and adult SES (Waldstein et al., 2017) are related to greater white matter lesion burden in adults. Little is known however about the relation between SES and white matter integrity, and the present literature is equivocal.

At least two studies found no relation between SES and white matter microstructure (i.e., integrity) in children (Chiang et al., 2011; Jednorog et al., 2012), although one of those studies found that children from higher SES environments were more likely to inherit greater fractional anisotropy (FA) in several brain regions (Chiang et al., 2011). Conversely, at least two other studies found that higher levels of SES in children are associated with greater white matter integrity in several fiber tracts (Ursache and Noble, 2016; Dufford and Kim, 2017). One additional study in children found significant relations between SES and FA in certain white matter tracts, but these results were in the unexpected direction in that higher SES was linked to lower FA (Noble et al., 2013). Although the literature is limited, associations between lower SES in adulthood and poorer white matter integrity have also been found in both neurological disease (Teipel et al., 2009) and non-clinical (Piras et al., 2011; Gianaros et al., 2013; Johnson et al., 2013) adult populations. Inconsistencies in the literature could be due to several factors, such as differences in chronological age, sociodemographic makeup of the samples, and overall white matter maturation across study samples.

The majority of SES-white matter integrity findings have been demonstrated in major, localized white matter fiber tracts, such as the superior longitudinal fasciculus (Gianaros et al., 2013; Noble et al., 2013; Dufford and Kim, 2017) and the cingulum bundle (Noble et al., 2013; Ursache and Noble, 2016; Dufford and Kim, 2017). However, the unique constellation of brain regions affected by SES differs across studies, and there may be regional specificity to the relation between SES and white matter integrity. For instance, white matter integrity of the temporal lobe may be differentially important in the context of SES (Teipel et al., 2009; Piras et al., 2011). More research is needed to determine if relations between SES and FA are uniform to the entire brain, or regionally specific.

Previous studies have also reported associations between self-identified race and brain health endpoints. In the United States, it is well documented that African Americans experience a disproportionate burden of poor clinical brain health compared to other racial/ethnic groups (Harwood and Ownby, 2000; Mozaffarian et al., 2016). Disparities in stroke risk are most pronounced, particularly during middle adulthood, such that African Americans are 3–4 times more likely than Whites to experience stroke by age 45 (Morgenstern et al., 1997). Racial disparities are also found in the frequency and severity of white matter lesions (Liao et al., 1997), as well as prevalence and incidence of Alzheimer's disease and other forms of dementia (Tang et al., 2001; Demirovic et al., 2003). African Americans also have greater burdens of vascular risk factors than their White counterparts, including obesity (Wang and Beydoun, 2007), diabetes mellitus (LaVeist et al., 2009), and hypertension (Hertz et al., 2005), which may deleteriously affect brain health. Despite evidence for racial disparities across a broad range of brain health outcomes, to our knowledge, relations of self-identified race with white matter integrity have not been examined in community-dwelling samples.

Considerable evidence suggests that aging is associated with deterioration of white matter as demonstrated by decreases in FA (Salat et al., 2005). Age-related decreases in FA have been found to differ by brain region (for a review see Raz and Rodrigue, 2006), such that reductions in white matter FA are generally greater in the frontal white matter compared to the temporal, parietal, and occipital lobes (Head et al., 2004; Salat et al., 2005). Indeed, converging evidence suggests an anterior-posterior gradient of age-related FA decreases (Sullivan and Pfefferbaum, 2006).

Only one study has examined concurrent age-, race- and SES-related differences in white matter microstructure. Johnson et al. (2013) examined associations between SES (as indicated by a composite measure of occupational and educational attainment) and white matter integrity in cognitively normal younger (mean age = 33.3 years) and older adults (mean age = 66.2 years). After adjustment for age, sex, and IQ, they found age-related differences in white matter integrity across a wide range of brain regions. However, among the older adults only, higher SES was associated with greater white matter integrity in three frontal tracts: the right anterior corona radiata and bilateral white matter regions underlying the superior frontal gyri.

No studies have examined interactive relations among SES, race, and age with white matter integrity. This is notable because previous research has shown that these sociodemographic characteristics may have synergistic influences on brain and other health endpoints. For example, racial health disparities cannot be fully explained by SES (Williams et al., 2010), as demonstrated by Waldstein et al. (2017) who found that African

Americans of higher SES did not differ from lower SES African Americans with respect to their total brain and white matter lesion volumes. It is also plausible that SES-related brain health disparities are greater at later periods in the adult lifespan, given the relatively high prevalence of age-related diseases among individuals of lower SES (Williams et al., 2010). This is consistent with theories of cumulative disadvantage that have demonstrated an aggregation of inequity throughout the lifespan (O'Rand, 1996; Epel et al., 2018), suggesting that SES-brain disparities may be more profound at older ages.

Several physiological, behavioral, and psychosocial risk factors may be important to consider when investigating the relation between SES and white matter integrity. Risk factors for cardiovascular disease, such as obesity, hypertension, diabetes, cigarette smoking, and systemic inflammation, have a detrimental impact on brain health (Waldstein and Elias, 2015). In an important study conducted by Gianaros et al. (2013), adiposity and smoking status independently mediated the relation between SES and white matter integrity, with high-sensitivity C-reactive protein (CRP) accounting for much of the variance in those meditational paths. This is consistent with the literature showing links between SES and poorer cardiovascular health (Pollitt et al., 2005), and between cardiovascular health and white matter integrity (Wersching et al., 2010; Stanek et al., 2011; Gow et al., 2012). Depressive symptomatology has also been linked to indicators of poor brain health. Previous studies have demonstrated that depression is a risk factor for stroke morbidity and mortality (for a meta-analysis see Pan et al., 2011). Higher rates of depression among individuals with poorer socioeconomic conditions are also well-documented (Hackman et al., 2010), and late life depression is associated with the frequency and intensity of white matter abnormalities (for a review see Herrmann et al., 2008) and changes in white matter microstructure as measured by FA (Yang et al., 2007).

Given the prognostic importance of white matter integrity on functional and neurocognitive outcomes (Madden et al., 2009), we examined associations of SES with diffuse white matter integrity, an approach that has not been examined previously. We also examined potential moderating roles of self-identified race and age on the association between SES and FA of the brain's primary cortical regions, including the right (R) and left (L) frontal, temporal, parietal, and occipital lobes (**Figure 1**). The methodological approach of using lobar measures of white matter integrity has been used in other contexts (e.g., Voss et al., 2013; Roalf et al., 2015), as it allows researchers to examine general trends across the brain while making fewer comparisons than using all of the brain's white matter tracts. This methodology can expand the present literature using tract-based approaches.

We also ran sensitivity analyses to examine whether adjustment for several key biomedical (i.e., body mass index [BMI], hypertension, diabetes, CRP), behavioral (i.e., cigarette smoking), and psychosocial (i.e., depressive symptoms) risk factors changed the findings observed in the main analyses, suggesting mediating effects of these co-morbid factors. We chose to examine these risk factors due to their well-documented associations with SES (Kaplan and Keil, 1993; Lorant et al., 2003) and white matter integrity (Burgmans et al., 2010; Gons et al., 2011; Korgaonkar et al., 2011; Stanek et al., 2011; Zhang et al., 2014; Walker et al., 2017). Given that BMI may have non-linear associations with health outcomes (e.g., Laxy et al., 2017), both linear and quadratic BMI were examined. To assess whether overall white matter vascular burden eliminated significant effects, we also ran sensitivity analyses adjusting for whole-brain white matter lesion volume. Finally, exploratory analyses examined (1) models using three different SES indicators on regional FA and (2) independent and interactive relations of SES, race, and age on trace diffusion, which captures diffusion of water across three perpendicular orientations.

MATERIALS AND METHODS

Sample and Participants

Participants were drawn from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) SCAN study, an investigation of brain health disparities attributable to race and SES (Waldstein et al., 2017). HANDLS SCAN is an ancillary study of the larger HANDLS investigation, a prospective, epidemiologic study of race- and SES-related health disparities. The design and implementation of the HANDLS parent study has been described previously (Evans et al., 2010). Briefly, the HANDLS sample is a fixed cohort of community-dwelling adults living in 13 neighborhoods (contiguous census tracts) in Baltimore City. The census segments were pre-determined for their likelihood of yielding representative samples of participants who were African American and White, men and women, aged 30–64 years, and with annual household income above and below 125% of the 2004 federal poverty level. HANDLS SCAN data collection overlapped with the first and second follow-up of the parent study. The imaging subsample used in this study is representative of the larger HANDLS study with regards to years of education, poverty status, and sex (p's > 0.05), but is more likely to include White and younger participants relative to the overall study sample (p's < 0.05).

Participants were excluded from the HANDLS parent study if they were (1) outside of the age range of 30–64 years, (2) currently pregnant, (3) within 6 months of active cancer treatment (i.e., chemotherapy, radiation, or biological treatments), (4) diagnosed with AIDS, (5) unable to provide informed consent, (6) unable to provide data for at least five measures, (7) unable to provide valid government-issued identification or were currently without a verifiable address (Evans et al., 2010). In addition to these criteria, HANDLS SCAN excluded participants with a self-reported history of dementia, stroke, transient ischemic attack, other neurological disease (e.g., multiple sclerosis, Parkinson's disease, or epilepsy), carotid endarterectomy, terminal illness (e.g., metastatic cancer), HIV positive status, or MRI contraindications (e.g., indwelling ferromagnetic material).

The present study's sample consisted of 192 HANDLS SCAN participants who had complete data for all relevant sociodemographic (SES, race, age, and sex) and diffusion tensor imaging (DTI) data with no incidental clinical findings on MRI.

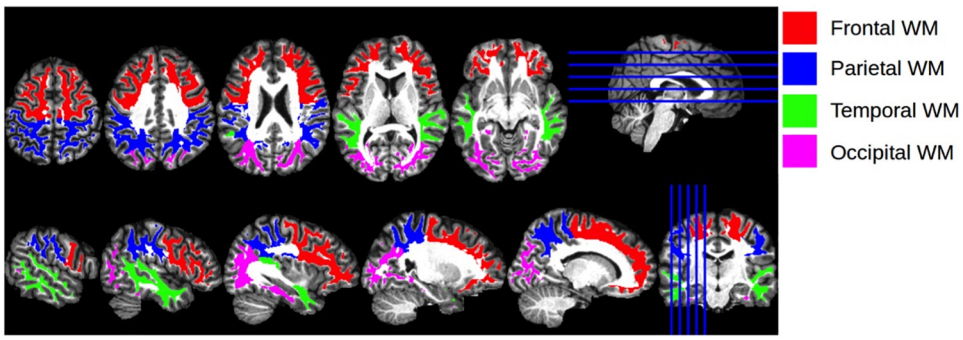

FIGURE 1 | Cortical Regions of Interest. Illustration of the anatomical regions of interest that were used for calculating regional mean fractional anisotropy and trace values. The four regions of interest, encoded with different colors for visualization, are shown overlaid on the T1 atlas image.

Procedure

HANDLS

HANDLS investigators recruited participants in each household by performing doorstep interviews, and inviting one or two eligible individuals per household to participate in the study. Successfully recruited and consented individuals were asked to complete an in-home 24-h dietary recall interview and a household survey inquiring about demographic, psychosocial, and physiological information. Participants were then scheduled for additional testing on the mobile research vehicles (MRVs). The Institutional Review Board (IRB) of the National Institute of Environmental Health Services, National Institutes of Health approved the HANDLS study.

HANDLS SCAN

HANDLS participants were invited to participate in HANDLS SCAN during their MRV visit. After successfully completing an eligibility screening inventory, participants provided written informed and HIPAA consent in accordance with Declaration of Helsinki. Participants were examined by a physician at the University of Maryland General Clinical Research Center for a brief medical evaluation to identify any acute medical problems since their last HANDLS visit, re-administer the MRI eligibility checklist, review current medications, and assess whether there were any contraindications precluding HANDLS SCAN testing. The subjects underwent MRI acquisition in the Department of Diagnostic Radiology and Nuclear Medicine at the University of Maryland School of Medicine. The IRBs of the University of Maryland, Baltimore and University of Maryland, Baltimore County approved the HANDLS SCAN study. Participants received $50 for their participation.

Measures

Sociodemographic Characteristics

Age (in years), sex (0 = female; 1 = male), poverty status, and education were assessed at study entry (data collection 2004–2009).

HANDLS investigators based their initial recruitment on a division of household income based on 125% of the 2004 federal poverty level. They effectively recruited a similar number of participants above and below the poverty level, as to appropriately represent individuals from low and moderate levels of income. Many HANDLS participants could not estimate their annual incomes, had no way to estimate their overall wealth, and/or were not consistently employed. Because HANDLS does not have an accurate estimate of income, a "poverty status" variable defined as household income above or below 125% of the 2004 federal poverty level adjusted for household size is used. Given the use of poverty status (a dichotomized variable in its original form), it was combined with a dichotomized measure of education to remain parsimonious. While there is controversy in the literature on how to best capture SES, we believe that our sample is best characterized by a composite measure of both education and income, which is consistent with prior recommendations (Adler et al., 1994).

Socioeconomic status was therefore comprised of: (1) dichotomous poverty status (0 = non-poverty; 1 = poverty); and (2) dichotomous years of education (0 = greater than or equal to 12 years; 1 = fewer than 12 years; Waldstein et al., 2017; Shaked et al., 2018, 2019). SES was dichotomized as high and low based on these two measures. Low SES was defined as having low education (<12 years), being below the poverty line, or both. Participants were classified as high SES if they were both living above the poverty level and had ≥12 years of education.

Sensitivity Variables

Depressive symptoms, cigarette smoking, BMI, hypertension, diabetes, and inflammation were assessed at the corresponding HANDLS visit. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression 20-item scale (Radloff, 1977). Cigarette smoking was assessed via self-report during the medical history assessment (coded as 0 = never used regularly, 1 = ever used regularly). BMI was computed as weight divided by height squared (kg/m^2) using height and weight obtained via calibrated equipment by a training technician. Hypertension and diabetes were dichotomous variables (coded as 0 = absent, 1 = present). Hypertension was determined by self-reported history, use of anti-hypertensive medications, or resting systolic or diastolic blood pressures ≥ 140 mm Hg or ≥ 90 mm Hg. Diabetes was

determined by a fasting blood glucose level of ≥ 126 mg/dl (assessed by standard laboratory methods at Quest Diagnostics in Chantilly, VA, United States[1]), self-reported history, or use of relevant medications. Inflammation was assessed with high-sensitivity CRP (mg/l) levels, which were measured from blood samples by immunoassay at the National Institutes of Aging or Quest Diagnostics using similar equipment and reagents. A HANDLS physician or nurse practitioner documented all clinical diagnostic data after a comprehensive physical examination and medical history.

Diffusion Tensor Imaging Acquisition and Processing

Cranial magnetic resonance images were acquired using a Siemens Tim-Trio 3.0 Tesla scanner within the Core for Translational Research in Imaging @ Maryland (C-TRIM), part of the Department of Diagnostic Radiology at University of Maryland Baltimore's School of Medicine. With regards to structural imaging, in addition to the standard brain imaging protocol, which includes axial T1, T2, FLAIR images, a high-resolution axial T1-weighted MPRAGE (TE = 2.32 ms, TR = 1900 ms, TI = 900 ms, flip angle = 9°, resolution = 256 × 256 × 96, FOV = 230 mm, sl. thick. = 0.9 mm) covering the entire brain was acquired. It was used both as an anatomic reference and to extract parameters of regional and whole brain volumes, and cortical thickness.

DTI was obtained using multi-band spin echo EPI sequence with a multi-band acceleration factor of three. Isotropic resolution images were acquired with an in-plane resolution of 2 × 2 mm and 2 mm slice thickness over a 22.4 cm FOV. A total of 66 slices at a TE = 122 ms, TR = 3300 ms, and flip angle = 90° were used. Bipolar diffusion scheme was used to reduce the effect of eddy currents. Diffusion weighting scheme was a 2-shell (b = 1000 and 2500 s/mm^2), optimized for uniform sampling of each shell and non-overlapping diffusion directions of 60 and 120 for each shell, respectively, and 6 b0 volumes. The image acquisition time was 10 min.

The raw diffusion weighted images (DWI) data was denoised using the Joint Linear Minimum Mean Squared Error denoising software (jLMMSE; Tristan-Vega and Aja-Fernandez, 2010). The diffusion tensor images were then reconstructed from denoised DWI data by fitting the tensor using multivariate linear fitting, while also performing motion correction using FSL' s "eddy correct" tool (Andersson and Sotiropoulos, 2016). FA and trace images were computed from the tensor image for each subject. FA, a widely known method for quantifying white matter integrity that is sensitive to the degree of myelination, density, and organization of white matter, was used to determine the degree of water diffusion directionality within brain tissue. The FA value, which measures the degree of anisotropy of the diffusion at a voxel, is computed from the variance of the average of the three eigenvalues of the diffusion tensor. FA values range from 0 to 1, with 0 reflecting completely unrestricted diffusion, and 1 reflecting completely restricted diffusion. Generally, healthier white matter integrity refers to more restricted diffusion, and thus for the purposes of this study, higher FA values are indicative of healthier white matter integrity. The trace value, which measures diffusivity, is computed by adding the eigenvalues of the diffusion tensor (Jones, 2008). After FA and trace images were computed from the tensor image for each participant, they were aligned to a common template space via deformable registration using a standard DTI template known as EVE (Wakana et al., 2004). In the present study, FA and trace from related cortical white matter subregions were averaged and summed, respectively, to create mean FA and total trace values for the larger brain regions, namely the R and L frontal, parietal, temporal, and occipital lobes. The cortical white matter subregions comprising the larger brain regions were drawn from previous literature (see Roalf et al., 2015).

Magnetic-Resonance Imaging-Assessed Lesion Volume

Structural MRI scans were preprocessed by removal of extra-cranial material on T1-weighted image using a multi-atlas registration-based method (Doshi et al., 2013), followed by bias correction (Tustison et al., 2010). A supervised learning based multi-modal lesion segmentation technique was applied to segment ischemic lesions (Zacharaki et al., 2008). The method involved co-registration of T1, T2, and FLAIR scans, histogram normalization to a template image, feature extraction, voxel wise label assignment using a model that was trained on an external training set with manually labeled ground-truth lesion masks, and false-positive elimination. The total white matter lesion volume was calculated for each subject from the segmented lesion mask.

Analytic Plan

All statistical analyses were performed by the Statistical Package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM: Corp.). Descriptive analyses were conducted to assess means, standard deviations, distributions, and linearity of variables. Main analyses were multiple linear regression to examine independent and interactive associations of age, race, and SES with white matter integrity of the R and L frontal, parietal, temporal, and occipital regions, adjusting for sex. Non-significant (at $p > 0.05$) interaction terms were removed by a backward elimination procedure (see Morrell et al., 1997).

Sensitivity and Exploratory Analyses

Subsequent, separate sensitivity analyses were conducted to assess respective contributions of BMI, hypertension, diabetes, CRP, cigarette smoking, depressive symptoms, and whole-brain white matter lesion volume as covariates in the aforementioned models. Due to missing data for depressive symptoms (n = 7 missing), CRP (n = 12 missing), and cigarette smoking (n = 25), data were imputed using a predictive mean matching method with the 'MICE' package in R (R Core Team, 2018), resulting in complete samples for all variables.

Using the same multiple regression models, supplemental exploratory analyses examined (1) independent and interactive

[1]http://www.questdiagnostics.com

relations of age, race, and individual SES (i.e., non-composite) indicators including poverty status, continuous education, and dichotomous education (0 = greater than or equal to 12 years/GED; 1 = less than 12 years) with FA; and (2) independent and interactive relations of age, race, and the SES composite with regional trace.

RESULTS

Demographics and Variable Characteristics

Table 1 shows demographic data and variable characteristics for the overall sample, and by SES and race. There were significant differences in age, sex, depressive symptoms, and cigarette smoking between those of low and high SES, wherein those of high SES, on average, were older, more likely to be male, have depressive symptoms, and smoke compared to those of low SES. Across race, Whites were, on average, older than African Americans. Those of high SES, on average, had higher FA in the frontal and occipital lobes bilaterally. There were no FA differences across racial groups.

Regression Analyses

There were no significant interactions between race, SES, or age on any of the cortical white matter regions (all p's > 0.05; see **Table 2**). There were significant main effects for SES for all regions, wherein individuals with low SES had lower FA in all cortical white matter regions (all p's < 0.05; see **Table 3**), demonstrating that individuals with lower SES had poorer white matter integrity throughout the entire brain. Significant main effects for age were found for nearly all regions (all p's > 0.05) such that older age was associated with lower FA in the cortical white matter regions, with the exception of the R temporal lobe, $\beta = -0.09$, $p = 0.208$, showing that poorer white matter integrity is related to older age almost uniformly across the brain. A main effect for sex was found for the R parietal lobe, wherein men had lower FA in this region, $\beta = -0.16$, $p = 0.029$. No significant main effects were found for race (all p's > 0.05).

Sensitivity Analyses

There were no significant main effects of hypertension (range of $\beta = -0.09$ to $\beta = -0.02$; all p's > 0.05), diabetes (range of $\beta = -0.04$ to $\beta = 0.07$; all p's > 0.05), linear BMI (range of $\beta = -0.06$ to $\beta = -0.01$; all p's > 0.05), quadratic BMI (range of $\beta = -0.08$ to $\beta = 0.06$; all p's > 0.05), CRP (range of $\beta = -0.05$ to $\beta = 0.04$; all p's > 0.05), cigarette smoking (range of $\beta = -0.06$ to $\beta = 0.001$; all p's > 0.05), or depressive symptoms (range of $\beta = -0.13$ to $\beta = 0.04$; all p's > 0.05) on any of the cortical white matter regions. All significant main effects of SES (see **Table 4** for associations of SES and regional FA outcomes after adjustment for sensitivity variables), age, and sex described previously remained significant after adjusting for hypertension, diabetes, linear and quadratic BMI, and CRP (all p's < 0.05). The significant association between SES and the R parietal lobe became non-significant following adjustment for depressive symptoms (attenuation to $p = 0.058$) and cigarette smoking (attenuation to $p = 0.06$), although the magnitude of changes in β were small (change from $\beta = -0.15$ to $\beta = -0.14$ following adjustment for either variable). Adding depressive symptoms and quadratic BMI also rendered main effects of sex with the R frontal and temporal lobes significant (all p's < 0.05), such that relative to women, men had lower FA in these regions.

There were significant associations between whole-brain white matter lesion volume and FA in the bilateral frontal, parietal, and occipital lobes (all p's < 0.05), but not the temporal lobes (p's > 0.05). Adjustment for whole-brain white matter lesion volume attenuated the significant relation between SES and the R parietal lobe FA (attenuation to $p = 0.169$; **Table 4**). Adding whole-brain white matter lesion volume also rendered main effects of sex with the R frontal and bilateral temporal lobes significant (all p's < 0.05), such that men had lower FA in these regions than women.

Exploratory Analyses

There were no significant interactions between age, race, and the various independent SES indicators (i.e., poverty status, continuous education, and dichotomous education) on any of the cortical white matter FA regions (all p's > 0.05). As displayed in **Table 5**, models with poverty status as the SES indicator yielded significant main effects for poverty status in the R frontal ($\beta = -0.20$, $p = 0.006$), L frontal ($\beta = -0.21$, $p = 0.004$), L parietal ($\beta = -0.15$, $p = 0.042$), R occipital ($\beta = -0.16$, $p = 0.031$), and L occipital ($\beta = -0.17$, $p = 0.026$) lobes, where individuals living in poverty had lower FA in these regions. A main effect for poverty status on the R parietal lobe was trending at $\beta = -0.14$, $p = 0.052$. In these models, age was related to all regions (β's ranged from -0.21 to -0.28, all p's < 0.01) except the R and L temporal lobes (p's > 0.05), wherein older age was related to lower FA. A main effect for sex was found for the R parietal lobe, wherein men had lower FA in this region, $\beta = -0.15$, $p = 0.031$. There were no significant main effects for race (all p's > 0.05). Models with dichotomous education as the SES indicator yielded a significant main effect for dichotomous education in the R occipital lobe ($\beta = -0.17$, $p = 0.018$). Significant main effects for age were found for nearly all regions (all p's < 0.05), such that older age was associated with lower FA, with the exception of the R temporal lobe ($\beta = -0.07$, $p = 0.319$). No main effects for sex or race were identified in these models. Models with continuous education as the SES indicator resulted in no significant main effects for continuous education, race, or sex. With the exception of the R temporal lobe ($\beta = -0.06$, $p = 0.418$), significant main effects for age were found for all regions (all p's < 0.05), such that older age was related with lower FA.

There were no significant interactions between age, race, and the composite SES indicator on any of the trace variables. As displayed in **Table 6**, SES was related to trace in the R frontal, L frontal, R temporal, L temporal, and L occipital lobes, wherein individuals with low SES had higher trace values. There were significant main effects for age and sex on all regions (all p's < 0.05) such that older individuals and men were more likely to have higher trace values. Relative to African Americans, Whites had higher trace values in the R and L parietal lobes.

TABLE 1 | Demographic and health variables for the overall sample and by SES and race.

	Overall (*N* = 192)	High SES (*n* = 99)	Low SES (*n* = 93)		AA (*n* = 77)	White (*n* = 115)	
Variable	**M (SD) or *n* (%)**	**M (SD) or *n* (%)**	**M (SD) or *n* (%)**	p_1	**M (SD) or *n* (%)**	**M (SD) or *n* (%)**	p_2
Age, y	52.03 (9.24)	53.99 (9.60)	49.95 (8.41)	0.002	50.28 (9.87)	53.21 (8.65)	0.031
AA	77 (40.1%)	33 (33.3%)	44 (47.3%)	0.049	–	–	–
Female	107 (55.75)	47 (47.5%)	60 (64.5%)	0.017	46 (59.7%)	61 (53.0%)	0.362
Low SES	95 (48.4%)	–	–	–	44 (57.1%)	49 (42.6%)	0.049
Hypertension	88 (45.8%)	51 (51.5%)	37 (39.8%)	0.104	39 (50.6%)	49 (42.6%)	0.276
Diabetes	30 (15.6%)	18 (18.2%)	12 (12.9%)	0.317	13 (16.9%)	17 (14.8%)	0.696
BMI, kg/m^2	29.57 (6.43)	29.95 (6.26)	29.16 (6.61)	0.398	29.66 (6.40)	29.50 (6.47)	0.868
CRP, mg/l	5.71 (10.12)	4.81 (7.87)	6.75 (12.36)	0.195	4.98 (7.45)	6.80 (13.12)	0.222
Cigarettes (ever)	139 (72.4%)	67 (67.7%)	72 (77.4%)	0.022	83 (72.2%)	77 (72.7%)	0.549
CES-D score	15.93 (11.49)	14.22 (10.60)	17.74 (12.17)	0.034	16.36 (12.07)	15.29 (10.62)	0.528
WMLV (cc)	1,294 (2,243)	1,210 (1,973)	1,385 (2,513)	0.594	1.188 (1,721)	1,431 (2,850)	0.431
R Frontal, FA	0.235 (0.013)	0.237 (0.011)	0.232 (0.014)	0.006	0.233 (0.013)	0.235 (0.013)	0.306
L Frontal, FA	0.234 (0.014)	0.237 (0.012)	0.232 (0.014)	0.009	0.233 (0.013)	0.235 (0.014)	0.349
R Temporal, FA	0.249 (0.014)	0.250 (0.014)	0.247 (0.014)	0.075	0.248 (0.012)	0.245 (0.015)	0.811
L Temporal, FA	0.241 (0.014)	0.243 (0.013)	0.239 (0.015)	0.064	0.241 (0.012)	0.241 (0.015)	0.849
R Parietal, FA	0.228 (0.015)	0.229 (0.014)	0.227 (0.016)	0.418	0.229 (0.015)	0.227 (0.015)	0.344
L Parietal, FA	0.232 (0.013)	0.233 (0.013)	0.230 (0.014)	0.055	0.231 (0.013)	0.232 (0.014)	0.894
R Occipital, FA	0.205 (0.013)	0.207 (0.013)	0.202 (0.013)	0.010	0.204 (0.011)	0.205 (0.014)	0.694
L Occipital, FA	0.203 (0.014)	0.205 (0.012)	0.200 (0.015)	0.019	0.203 (0.013)	0.204 (0.014)	0.642

y = years; AA = African American; SES = socioeconomic status; BMI = body mass index; CRP = C-reactive protein; CES-D = Center for Epidemiologic Studies-Depression scale; WMLV = white matter lesion volume; R = right; L = left; FA = fractional anisotropy; p_1 = value for the difference between those high and low SES; p_2 = value for the difference between African Americans and Whites; independent samples t-tests were used for continuous variables (all equal variances assumed) and one-way ANOVAs were used for categorical variables. Fractional anisotropy values range from 0 to 1, with 0 reflecting completely unrestricted diffusion, and 1 reflecting completely restricted diffusion.

TABLE 2 | Sociodemographic variables and regional fractional anisotropy: full models.

	Outcome (Fractional Anisotropy; *N* = 192)															
	R Frontal		L Frontal		R Temporal		L Temporal		R Parietal		L Parietal		R Occipital		L Occipital	
Predictor	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2
SES∗Age∗Race	−0.02	0.000	−0.15	0.000	0.20	0.001	0.01	0.000	0.58	0.005	0.32	0.001	−0.18	0.000	0.22	0.001
Age∗Race	−0.54	0.006	−0.27	0.001	−0.42	0.003	−0.38	0.003	−0.44	0.004	−0.48	0.004	−0.27	0.002	−0.54	0.006
Age∗SES	−0.18	0.001	0.08	0.000	−0.38	0.003	−0.10	0.000	−0.41	0.003	−0.24	0.001	−0.15	0.000	−0.44	0.004
Race∗SES	−0.08	0.000	0.20	0.000	−0.29	0.001	−0.09	0.000	−0.58	0.004	−0.32	0.001	0.11	0.000	−0.38	0.002
Age	−0.21	0.013	−0.27*	0.020	−0.01	0.000	−0.14	0.005	−0.20	0.011	−0.21	0.012	−0.21	0.013	−0.11	0.003
Race	0.49	0.004	0.15	0.000	−0.44	0.003	0.42	0.003	0.45	0.003	0.43	0.003	0.26	0.001	0.57	0.005
SES	−0.07	0.000	−0.38	0.002	0.24	0.001	−0.08	0.000	0.24	0.001	0.01	0.000	−0.09	0.000	0.26	0.001
Sex	−0.13	0.016	−0.08	0.005	−0.14	0.017	−0.14	0.017	−0.16*	0.023	−0.09	0.008	−0.09	0.007	−0.12	0.014

*SES = socioeconomic status; R = right; L = left. Full models reflect the models that include all interactions, prior to the backward elimination procedure. *$p < 0.05$. Data reflect standardized regression coefficients (β) and semipartial correlations squared (sr^2).*

DISCUSSION

To our knowledge, this is the first study to examine independent and interactive relations between SES, race, and age with white matter integrity in primary cortical regions. Our findings demonstrate sociodemographic disparities in the brain's white matter microstructure, which may have implications for cognitive, functional, and neurological disease-related outcomes. Although no significant interactions were observed, our results suggest poorer diffuse white matter integrity, on average, for individuals of lower SES. There were no differences in white matter integrity between racial groups and, as expected, poorer white matter integrity was associated with older age. When examining additional SES indicators, poverty status revealed as most prominently related to SES. Further exploratory analyses showed greater diffusion (captured via trace) in individuals with lower SES in the R and L frontal, R and L temporal, and L occipital lobes. Greater diffusion throughout the brain was also associated with older age and male sex, as well as with being White for the parietal lobes.

TABLE 3 | Sociodemographic variables and regional fractional anisotropy: final models.

	Outcome (Fractional Anisotropy; *N* = 192)															
	R Frontal		L Frontal		R Temporal		L Temporal		R Parietal		L Parietal		R Occipital		L Occipital	
Predictor	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2
Age	−0.31***	0.088	−0.29***	0.078	−0.09	0.008	−0.18*	0.029	−0.26***	0.062	−0.28***	0.072	−0.28***	0.075	−0.24**	0.052
SES	−0.28***	0.069	−0.25**	0.058	−0.17*	0.026	−0.20**	0.035	−0.15*	0.020	−0.21**	0.041	−0.26***	0.061	−0.24**	0.050
Race	−0.09	0.008	−0.08	0.006	−0.02	0.000	0.01	0.000	0.04	0.002	−0.03	0.001	−0.04	0.002	−0.05	0.002
Sex	−0.13	0.016	−0.07	0.005	−0.14	0.018	−0.13	0.017	−0.16*	0.023	−0.09	0.008	−0.08	.007	−0.12	0.014

*SES = socioeconomic status; R = right; L = left. Final models reflect the models following the backward elimination procedure. *p < 0.05, **p < 0.01, ***p < 0.001. Data reflect standardized regression coefficients (β) and semipartial correlations squared (sr^2).*

TABLE 4 | Associations of the main effect of SES with regional fractional anisotropy, adjusted for sensitivity variables.

	Outcome (*N* = 192)															
	R Frontal		L Frontal		R Temporal		L Temporal		R Parietal		L Parietal		R Occipital		L Occipital	
Covariate	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2
Base model[a]	−0.28***	0.07	−0.25**	0.06	−0.17*	.03	−0.20**	0.04	−0.15*	0.02	−0.21**	0.04	−0.26***	0.06	−0.24**	0.05
Hypertension	−0.28***	0.08	−0.26**	0.06	−0.18*	0.03	−0.20**	0.04	−0.15*	0.02	−0.21**	0.04	−0.26***	0.07	−0.24**	0.05
Diabetes	−0.28***	0.08	−0.25**	0.06	−0.17*	0.03	−0.20**	0.04	−0.15*	0.02	−0.21**	0.04	−0.26***	0.06	−0.24**	0.05
BMI	−0.28***	0.08	−0.25**	0.06	−0.18*	0.03	−0.20**	0.04	−0.15*	0.02	−0.21**	0.04	−0.25**	0.06	−0.23**	0.05
BMI^2	−0.28***	0.08	−0.26**	0.06	−0.18*	0.03	−0.20**	0.04	−0.15*	0.02	−0.22**	0.04	−0.25**	0.06	−0.23**	0.05
CRP	−0.28***	0.08	−0.25**	0.06	−0.17*	0.03	−0.19*	0.04	−0.15*	0.02	−0.21**	0.04	−0.26**	0.06	−0.23**	0.05
Cigarettes	−0.28***	0.07	−0.25**	0.06	−0.16*	0.02	−0.20*	0.04	−0.14	0.02	−0.20**	0.04	−0.25**	0.06	−0.23**	0.05
CES-D	−0.26***	0.07	−0.24**	0.05	−0.16*	0.03	−0.19*	0.03	−0.14	0.02	−0.20**	0.04	−0.25**	0.06	−0.22**	0.05
WMLV	−0.24***	0.05	−0.21**	0.04	−0.15*	0.02	−0.16*	0.02	−0.10	0.01	−0.16**	0.03	−0.23**	0.05	−0.21**	0.04

*SES = socioeconomic status; BMI = body mass index; CRP = C-reactive protein; CES-D = Center for Epidemiologic Studies-Depression scale; WMLV = white matter lesion volume; R = right; L = left. Demonstration of the main effects of SES with regional fractional anisotropy in the additional models that include a sensitivity variable. *p < 0.05, **p < 0.01, ***p < 0.001. Data reflect standardized regression coefficients (β) and semipartial correlations squared (sr^2). [a]Base model includes SES, race, age, and sex.*

These results add to the limited literature demonstrating an SES-white matter integrity association in community-dwelling adults. As far as we are aware, this is the first study to demonstrate that the SES-white matter integrity link appears to be uniform across the brain's primary cortical regions, as opposed to differentially across particular lobes or hemispheres. The relation between SES and trace, which can be used to measure alterations in brain tissue (Bosch et al., 2012), was also fairly widespread, with the temporal lobes and R occipital lobe spared. These findings add to studies demonstrating an anterior-posterior diffusion gradient (Sullivan and Pfefferbaum, 2006; Bosch et al., 2012), as well as increased diffusivity in occipital regions in vulnerable clinical populations (Friese et al., 2010). These findings are consistent with prior literature finding a link between lower SES and compromised white matter integrity in children (Ursache and Noble, 2016; Dufford and Kim, 2017) and adults (Teipel et al., 2009; Piras et al., 2011; Gianaros et al., 2013; Takeuchi et al., 2018). These studies, however, focused on individual tracts, whereas this study examined these associations from a regional lobar perspective. Both approaches are vital for better understanding SES-white matter relations.

The association of lower SES with poorer diffuse white matter integrity is important given the adverse cognitive outcomes associated with reduced white matter integrity. There is ample evidence from clinical and normal aging samples demonstrating "disconnection syndromes," wherein compromised microstructure of the white matter tracts is thought to lead to poorer communication between brain regions, ultimately resulting in poorer cognitive function and more profound cognitive decline (O'Sullivan et al., 2001; Chanraud et al., 2010). This is relevant given the well-established literature demonstrating poorer performance, on average, on tests of cognitive function across a range of domains in individuals from lower SES homes (e.g., Singh-Manoux et al., 2005; Noble et al., 2007; Hackman and Farah, 2009; Shaked et al., 2018). While not examined directly here, perhaps SES-related differences on cognitive tests are, at least in part, explained by disparities in diffuse white matter integrity. Future studies should examine the potential mediating role of white matter integrity in the relation between SES and cognitive outcomes. Moreover, white matter microstructural properties (e.g., white matter integrity) are considered a proxy for brain reserve (Stern et al., 2018), which is defined as "neurobiological capital. . .that allows some people

TABLE 5 | SES indicators and regional fractional anisotropy: final models.

Variable	SES Interaction Term (All *N*s = 192)					
	Continuous Education		Dichotomous Education		Poverty Status	
	β	sr^2	β	sr^2	β	sr^2
R Frontal						
Age	−0.27***	0.069	−0.27***	0.070	−0.28***	0.076
SES	0.12	0.014	−0.13	0.015	−0.20**	0.037
Race	−0.12	0.014	−0.13	0.017	−0.09	0.007
Sex	−0.10	0.009	−0.09	0.009	−0.11	0.013
L Frontal						
Age	−0.25**	0.060	−0.26**	0.062	−0.27***	0.070
SES	0.09	0.008	−0.11	0.012	−0.21**	0.045
Race	−0.11	0.011	−0.12	0.014	−0.07	0.005
Sex	−0.04	0.002	−0.04	0.002	−0.06	0.004
R Temporal						
Age	−0.06	0.003	−0.07	0.005	−0.08	0.006
SES	0.01	0.000	−0.09	0.008	−0.12	0.014
Race	−0.03	0.001	−0.05	0.002	−0.01	0.000
Sex	−0.11	0.011	−0.12	0.013	−0.13	0.015
L Temporal						
Age	−0.15*	0.021	−0.16*	0.023	−0.16	0.023
SES	0.09	0.007	−0.12	0.013	−0.12	0.012
Race	−0.02	0.000	−0.03	0.001	0.01	0.000
Sex	−0.11	0.012	−0.11	0.012	−0.12	0.013
R Parietal						
Age	−0.23**	0.051	−0.23**	0.051	−0.25**	0.059
SES	0.05	0.002	−0.03	0.001	−0.14^	0.018
Race	0.02	0.001	0.02	0.000	0.05	0.002
Sex	−0.14	0.018	−0.13	0.018	−0.15*	0.023
L Parietal						
Age	−0.25**	0.058	−0.25**	0.058	−0.26***	0.064
SES	0.09	0.007	−0.08	0.006	−0.15*	0.021
Race	−0.05	0.003	−0.06	0.003	−0.03	0.009
Sex	−0.07	0.005	−0.07	0.004	−0.08	0.006
R Occipital						
Age	−0.25**	0.058	−0.26***	0.063	−0.26***	0.062
SES	0.10	0.010	−0.17*	0.028	−0.16*	0.023
Race	−0.07	0.005	−0.09	0.007	−0.04	0.002
Sex	−0.06	0.003	−0.06	0.003	−0.07	0.004
L Occipital						
Age	−0.20**	0.039	−0.21**	0.041	−0.21**	0.043
SES	0.10	0.009	−0.12	0.014	−0.17*	0.025
Race	−0.07	0.005	−0.08	0.007	−0.04	0.002
Sex	−0.10	0.009	−0.10	0.009	−0.11	0.012

*SES = socioeconomic status; R = right; L = left. Final models reflect the models following the backward elimination procedure. ^p = 0.05, *p < 0.05, **p < 0.01, ***p < 0.001. Data reflect standardized regression coefficients (β) and semipartial correlations squared (sr^2).*

to better cope with brain aging and pathology than others (p. 3, Stern et al., 2018)." Within this context our findings of altered white matter integrity suggest that individuals from lower SES homes have lower levels of such reserve. Future studies should assess if less of this form of reserve puts low SES individuals at greater risk for more profound age- and disease-related changes, such as steeper cognitive decline in the face of Alzheimer's disease pathology.

Exploratory analyses showed that poverty status and education were differentially related to white matter integrity across the examined brain regions. Prior literature has noted that different socioeconomic influences play varying roles in brain plasticity (Farah, 2017). Poverty status seems to represent widespread correlates of economic status, such as material resources and financial hardships, as well as nutrition and toxin exposure. While also a proxy for resources and opportunity, educational attainment may better capture school-related factors like language stimulation and literacy (although quantity of formal education is not equivalent to education quality). The lack of findings with education alone is notable given the literature demonstrating relations between educational attainment and white matter integrity (Teipel et al., 2009; Chiang et al., 2011; Gianaros et al., 2013; Johnson et al., 2013; Noble et al., 2013). One potential reason for these discrepant findings is that some studies (Chiang et al., 2011; Johnson et al., 2013) used composite indices, and it is therefore unknown if education was the primary driver in those studies' findings. Another possible explanation is the nature of the study samples. Our sample was comprised of a sociodemographically diverse group of urban-dwelling adults, while one study was conducted in children (Noble et al., 2013), and others had no (Teipel et al., 2009) or a smaller proportion of (Gianaros et al., 2013) African Americans in their sample. Given that poverty status captured more of the findings than education alone in our study, perhaps relative to educational attainment, poverty status is a greater influencer of disparities in white matter integrity in this socioeconomically and racially diverse sample of adults. That said, given that the SES composite revealed more significant findings and larger effect sizes than findings with poverty status alone (see **Tables 3**, **5**), perhaps for adults, the cumulative nature of education and poverty status is a relatively stronger determinant of disparities in white matter integrity.

While it is evident that there are individual differences in white matter health across SES groups, the biopsychosocial factors that are most important for this variability are not well established. It is known, for instance, that cardiovascular risk factors like hypertension and cigarette smoking adversely impact white matter integrity (e.g., Gianaros et al., 2013; Wang et al., 2015), but other factors like depression and stress have equivocal results (Gianaros et al., 2013; Choi et al., 2014; Hermens et al., 2018). These inconsistent findings are perhaps surprising given the well-established relations of stress and depression on inflammation, which is closely related to white matter integrity (Wersching et al., 2010; Gianaros et al., 2013; Walker et al., 2017).

The sensitivity analyses found that adjustment of several common cardiovascular and inflammatory risk factors did not attenuate significant effects of SES on FA of the primary cortical regions, nor were they significantly related to FA in these regions. The lack of attenuation could be due to the absence of relations between SES and most of the health variables (**Table 1**). These findings are perhaps counter-intuitive given the literature demonstrating disparities in cardiovascular and inflammatory

TABLE 6 | Sociodemographic variables and regional trace: final models.

	Outcome (Trace; *N* = 192)															
	R Frontal		L Frontal		R Temporal		L Temporal		R Parietal		L Parietal		R Occipital		L Occipital	
Predictor	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2	β	sr^2
Age	0.52***	0.252	0.53***	0.263	0.38***	0.132	0.34***	0.106	0.45***	0.187	0.46***	0.200	0.41***	0.155	0.41***	0.154
SES	0.20**	0.036	0.16*	0.023	0.19**	0.032	0.16*	0.022	0.07	0.005	0.11	0.011	0.12	0.014	0.20**	0.035
Race	−0.02	0.000	−0.05	0.003	−0.17*	0.027	−0.10	0.009	−0.20**	0.038	−0.15*	0.020	−0.10	0.009	0.07	0.004
Sex	0.26***	0.064	0.24***	0.057	0.17**	0.029	0.23**	0.050	0.32***	0.096	0.30***	0.086	0.22**	0.045	0.22**	0.045

*SES = socioeconomic status; R = right; L = left. Final models reflect the models following the backward elimination procedure. *p < 0.05, **p < 0.01, ***p < 0.001. Data reflect standardized regression coefficients (β) and semipartial correlations squared (sr^2).*

risk factors across socioeconomic groups (Adler et al., 1994; Pollitt et al., 2005). However, they may also reflect prior literature demonstrating complex interactive relations of SES, race, and/or gender with respect to cardiovascular risk factors (Williams et al., 2010; Waldstein et al., 2016). In that regard, it has been noted across multiple investigations that higher SES African Americans often have worse cardiovascular risk profiles than lower SES African Americans, perhaps reflecting the "diminishing returns" hypothesis (Farmer and Ferraro, 2005), which posits that African Americans may not benefit as much as Whites from higher levels of SES.

Although it is possible that other vascular and biomedical risk factors are implicated in the observed SES-white matter associations, it is also possible that adjustment for individual risk factors does not fully capture the cumulative burden of vulnerability associated with lower SES across the lifespan. Research has shown an association between early life adversity and lower adult SES (Metzler et al., 2017), and that children of lower SES, on average, have poorer white matter integrity than children of higher SES (Ursache and Noble, 2016; Dufford and Kim, 2017), although results have been inconsistent across studies (Chiang et al., 2011; Jednorog et al., 2012). This suggests that SES-related differences in FA may begin in childhood, and perhaps, continue to widen due to lifelong exposure to various biopsychosocial risk factors, including inadequate nutrition (Hartline-Grafton and Dean, 2017), lesser access to health care (Lazar and Davenport, 2018), chronic stress (Baum et al., 1999), environmental toxins (Evans and Kantrowitz, 2002), and greater overall burden of disease (Pathirana and Jackson, 2018).

Adjustment for depressive symptoms, cigarette smoking, and whole-brain white matter lesion volume negated associations between SES and FA in the R parietal lobe. The size of the SES effect however was largely unchanged following adjustment for depressive symptoms and cigarette smoking (sr^2 = 0.02, with and without adjustment for these variables; see **Table 4**). Previous DTI research has demonstrated that major depressive disorder is significantly associated with decreased FA in left hemisphere regions (Zou et al., 2008), consistent with other neuroimaging research suggesting a left-hemisphere dominance for symptoms of depression (Morris et al., 1996). The lack of relation between depressive symptoms and left hemisphere regions may be due to not assessing for a validated diagnosis of major depressive disorder, but rather depressive symptom severity. More research is needed to identify psychosocial and behavioral risk factors that are associated with reduced FA, and how they operate within the mechanistic pathways by which lower SES adversely relates to white matter structure.

Following adjustment for whole-brain white matter lesion volume, the size of the SES effect on the R parietal lobe reduced from sr^2 = 0.02 to sr^2 = 0.01 (**Table 4**). Although small, this reduction may suggest that overall maturation and/or white matter vascular burden is implicated in SES-related FA differences in this region. That said, significant associations between SES and FA in other cortical white matter regions remained significant, indicating that SES-related difference in white matter integrity throughout the brain exist above and beyond overall white matter maturation. It is worth noting that out of all the cortical regions examined, the R parietal lobe, while significant, had the weakest relation with SES in the base models. The relation between SES and the R parietal lobe may therefore not be strong enough to maintain significance following the loss of power.

Consistent with past research (Salat et al., 2005), the present study found that older age was associated with significantly lower FA and higher trace throughout the brain, with the exception of the R temporal lobe for FA. It is possible that in an older sample, greater age would also be associated with lower R temporal lobe FA, or that further region-specific differences would be observed. A previous study reported that higher SES (versus lower SES) was associated with greater white matter integrity in three frontal tracts in older (i.e., 66 years), but not younger (i.e., 33 years) participants (Johnson et al., 2013). The present study's finding that age did not moderate associations between SES and white matter integrity may therefore reflect our relatively younger sample. It is also possible that differences in SES measurement accounted for these differences. The previous study used a composite of educational attainment and occupation, whereas our study used a composite of educational attainment and poverty status. Indeed, SES is a multidimensional construct (Braveman et al., 2005), and different socioeconomic indicators may be differentially associated with brain outcomes. Interestingly, widespread associations were also found between sex and trace, where relative to women, men had greater levels of diffusion throughout the entire brain. This is consistent with a recent study of young adults (*N* = 1,216) finding a significant sex by SES interaction, where among those with

higher levels of family income and level of education, men had higher mean diffusivity (an average of trace) relative to women (Takeuchi et al., 2018). Perhaps with a larger sample size and greater statistical power, our study would have produced similar results. Future studies should seek to determine mediators and additional moderators of the trace-sex relation, as to better understand why men are vulnerable to greater diffusivity, but not poorer white matter integrity.

Given that the literature on racial differences in white matter microstructure is limited, our study, which found non-significant independent and moderating effects of self-identified race with FA in a community-dwelling sample, represents a novel contribution to the literature. The lack of significant interactive relations between race and SES is surprising, given previous findings in the HANDLS SCAN sample demonstrating such an interaction with white matter lesion volume (Waldstein et al., 2017) and volumes of stress-related brain regions (Shaked et al., 2019). Further, irrespective of SES, African Americans experience greater burden of stroke (Morgenstern et al., 1997), white matter lesions (Liao et al., 1997), and dementia than their White counterparts (Mayeda et al., 2016), as well as exposure to biomedical (e.g., hypertension, diabetes mellitus), psychosocial (e.g., social discrimination, chronic stress), and environmental (e.g., geographic segregation, toxin exposure) risk factors that influence brain and cognitive health across the lifespan (Glymour and Manly, 2008; Williams et al., 2010). One possibility for the null race-related findings is that social risk factors specifically linked to self-identified race, such as racial discrimination, are unrelated to white matter integrity, but exert influence on global and regional brain and white matter lesion volumes. This possibility, however, is highly speculative and needs to be examined directly in future studies. Unexpectedly, relative to African Americans, White individuals had greater diffusion in the parietal lobes. One explanation for these findings is that Whites are significantly older than the African Americans in our sample (p = 0.03, Whites = 53 years, African Americans = 50 years). As noted, age was strongly related to greater diffusion (**Table 6**; βs ranged from 0.34 to 0.53), and the race effects may be due to residual confounding of age. Further research on biopsychosocial factors that are uniquely associated with white matter integrity and diffusivity could help clarify potential race differences in DTI indices.

This study had notable strengths. The HANDLS investigation was explicitly designed to disentangle SES- and race-related health disparities, and therefore our present study contained a wide range of SES among African American and White community-dwelling adults. Our study used a SES composite comprised of two key indicators, educational attainment and poverty status, which are implicated in brain health and aging. This was the first study to examine potential moderating effects of race and age on the association between SES and FA in key cortical regions and expanded on previous research by examining how further adjustment of relevant biopsychosocial risk factors changed associations of SES and FA.

This study also had several limitations. The results may be specific to adults living within the urban environment of Baltimore City. Future studies should examine associations of sociodemographic factors with FA in other racial/ethnic minorities and participants living in non-urban environments. Moreover, while our imaging subsample was representative of the larger HANDLS sample with regards to poverty status, years of education, and sex, the imaging subsample was significantly more likely to include younger and White participants. Conclusions regarding race and age effects should therefore be generalized with caution to the overall HANDLS sample. Also, while we examined the influence of several cardiovascular risk factors, we did not account for the duration of illnesses, influences of different classes of medication, and medication adherence, as HANDLS did not collect this information. Our composite measure of SES did not assess other socioeconomic indicators, such as occupational status, wealth, or income. Future studies should evaluate how additional SES indicators influence white matter microstructure in a socioeconomically diverse sample of adults. Also, we did not directly examine outcome variables such as cognitive ability and decline, which are important when considering the functional implications of our findings. Future studies should examine the potential mediating role of DTI outcomes in SES disparities of cognition and other functional outcomes related to white matter integrity. Finally, our study was cross-sectional and therefore did not examine within-subject age-related changes in white matter integrity. Longitudinal studies should examine how SES and self-identified race predict age-related degradation in FA.

In sum, lower SES was associated with poorer white matter integrity uniformly across the brain's primary cortical regions, and with greater diffusion in the R and L frontal, R and L temporal, and L occipital lobes. These findings may reflect, at least in part, disproportionate exposure to biopsychosocial risk factors among those of lower SES, and may translate into more pronounced risk for age- and/or disease-related cognitive decline. Subsequent adjustment of vascular and inflammatory risk factors did not result in attenuation of SES effects anywhere in the brain, although depressive symptoms, smoking status, and white matter lesion volume negated the relation between SES and the R parietal lobe. Consistent with previous research, older age was also associated with poorer white matter integrity and greater diffusivity throughout the primary cortical regions. No differences in white matter integrity were found between self-identified African Americans and Whites, nor did our findings reveal significant interactions among SES, race, and age with white matter integrity in any region. The profound differences in white matter microstructure across SES groups is very relevant given the adverse cognitive, functional, and neurological-disease outcomes associated with poorer white matter integrity. Ideally, this research will encourage researchers and society at large to promote brain health across the socioeconomic spectrum. Future research is needed to identify mechanistic determinants of the SES-white matter relation as to promote targeted interventions and prevention efforts.

DATA AVAILABILITY

Data are available upon request to researchers with valid proposals who agree to the confidentiality agreement as required by our Institutional Review Boards. We publicize our policies

on our website[2]. Requests for data access may be sent to AZ (co-author) or the study manager, Jennifer Norbeck at norbeckje@mail.nih.gov.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of Maryland, Baltimore and the University of Maryland, Baltimore County Institutional Review Boards with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

DS, DL, and SW: general conception. ME, AZ, and SW: parent study design. DS and DL: data analysis and drafting the manuscript. DS, DL, LK, CD, RG, SS, GE, ME, AZ, and SW: final preparation of the article, data collection, preparation, and interpretation.

[2] https://handls.nih.gov/

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[3] https://www.nih.gov

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frontiers in Human Neuroscience

PERSPECTIVE
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Applying a Women's Health Lens to the Study of the Aging Brain

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A major challenge in neuroscience is to understand what happens to a brain as it ages. Such insights could make it possible to distinguish between individuals who will undergo typical aging and those at risk for neurodegenerative disease. Over the last quarter century, thousands of human brain imaging studies have probed the neural basis of age-related cognitive decline. "Aging" studies generally enroll adults over the age of 65, a historical precedent rooted in the average age of retirement. A consequence of this research tradition is that it overlooks one of the most significant neuroendocrine changes in a woman's life: the transition to menopause. The menopausal transition is marked by an overall decline in ovarian sex steroid production—up to 90% in the case of estradiol—a dramatic endocrine change that impacts multiple biological systems, including the brain. Despite sex differences in the risk for dementia, the influence that biological sex and sex hormones have on the aging brain is historically understudied, leaving a critical gap in our understanding of the aging process. In this *Perspective* article, we highlight the influence that endocrine factors have on the aging brain. We devote particular attention to the neural and cognitive changes that unfold in the middle decade of life, as a function of reproductive aging. We then consider emerging evidence from animal and human studies that other endocrine factors occurring earlier in life (e.g., pregnancy, hormonal birth control use) also shape the aging process. Applying a women's health lens to the study of the aging brain will advance knowledge of the neuroendocrine basis of cognitive aging and ensure that men and women get the full benefit of our research efforts.

Keywords: cognitive aging, neuroimaging, women's health, sex steroid hormones, estradiol, menopause, reproductive aging, memory

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INTRODUCTION

An overarching goal of cognitive neuroscience is to understand the complexities of human brain function across the lifespan. To make sense of cognition and behavior, scientists test hypotheses on a "representative" sample of individuals that are assumed to generalize to a larger population. Here, we argue that it is imperative for scientists to reconsider what constitutes a representative sample.

A pressing problem in the biomedical sciences is the under-representation of females in experimental designs. For the past half-century, the convention in preclinical research has been to study male animals, at the near-exclusion of females. Females were considered "too variable" (Beery and Zucker, 2011) despite empirical evidence that variability within each sex is the same

across a broad range of phenotypes (Prendergast et al., 2014). In 2016 in the US, this sex bias in biomedical research was addressed at the national level when Janine Clayton (Director, Office of Women's Health Research) pioneered the National Institute of Health's mandate requiring the inclusion of female and male animals in preclinical science (Clayton and Collins, 2014). The goal of the mandate is to ensure that future studies are balanced by sex, a key step to bolstering our understanding of sex similarities and sex differences across the biomedical sciences.

In human neuroscience, the problem is more subtle. While the majority of studies enroll both men and women, women do not benefit equally from our research efforts. Scientists often overlook sex-specific variables, a bias that seeps into our study design and analyses and impedes our basic understanding of the brain. In this *Perspective* article, we address one domain that is often unaccounted for in human neuroscience: the influence of sex steroid hormones on the brain. This is surprising, given that the brain is an endocrine organ and in animal studies, the effects of sex hormones on the central nervous system are extensive, ranging from changes in gene expression to alterations in behavior (McEwen, 2001). Across a typical menstrual cycle (occurring every 25–30 days), naturally cycling women experience a ∼12-fold increase in estrogen and an ∼800-fold increase in progesterone. Later in life, women experience a more abrupt change in sex steroid hormone production as they transition through menopause. Further, sex hormone production is chronically suppressed in the 100 million women worldwide using oral hormonal contraceptives (OCs). For men, testosterone production shows a gradual, protracted decline beginning in the mid-30s and continuing throughout life. How do these shifts in hormone production shape the brain? Do endocrine factors influence how the brain ages? The field of human neuroscience has not adequately addressed these questions and women may be disproportionately disadvantaged by this oversight.

Below, we describe animal and human evidence that sex hormones regulate the structure and function of brain regions critical to learning and memory. We focus on the implications of this work for understanding the neurobiological mechanisms of cognitive aging. Moving forward, the field of human cognitive neuroscience must consider features (e.g., the menstrual cycle, menopause, pregnancy, and OC use) that are relevant to half of our study population. If not, we will be left with an inadequate understanding of the aging brain and will risk the health of half of the world's population.

THE NEUROENDOCRINE BASIS OF COGNITIVE AGING

A major challenge in neuroscience is to understand what happens to a brain as it ages. Distinguishing between individuals who undergo typical aging from those at risk for neurodegenerative disease is critical for targeting early interventions to high-risk individuals. Over the last quarter century, thousands of human brain imaging studies have probed the neural basis of age-related cognitive decline. These studies generally enroll adults over the age of 65, a historical precedent rooted in the average age of retirement. A consequence of this research tradition is that it overlooks one of the most significant neuroendocrine changes in a woman's life: the transition to menopause. The menopausal transition is marked by an overall decline in ovarian sex steroid production—up to 90% in the case of estradiol—a dramatic endocrine change that impacts multiple biological systems, including the brain (Morrison et al., 2006).

In the context of cognitive aging, female reproductive aging presents a critical yet understudied factor (**Figure 1**) that is likely essential for understanding the early processes that contribute to age-related cognitive decline and ultimately dementia risk. Indeed, growing evidence from animal studies indicates that sex steroids including estradiol, progesterone, and testosterone, play a substantial role in supporting the structure and function of brain regions relevant to cognitive aging (Jacobs and Goldstein, 2018).

Sex Hormone Action in Memory Circuitry

The actions of estrogen in the brain are in large part dependent on the location of estrogen receptors (ERs; McEwen and Alves, 1999). At the cellular level, estrogen, primarily in the form of 17β-estradiol, facilitates synaptogenesis, protects against oxidative stress, and regulates neuromodulators including serotonin, norepinephrine, dopamine, and acetylcholine (Becker, 1990; Thompson and Moss, 1994; McEwen and Alves, 1999; McEwen et al., 1997; McEwen and Alves, 1999; Walf and Frye, 2006; Wang et al., 2010; Chisholm and Juraska, 2012; Bean et al., 2014; Galvin and Ninan, 2014; Almey et al., 2015; Hara et al., 2015, 2016; Rossetti et al., 2016; Frick et al., 2018).

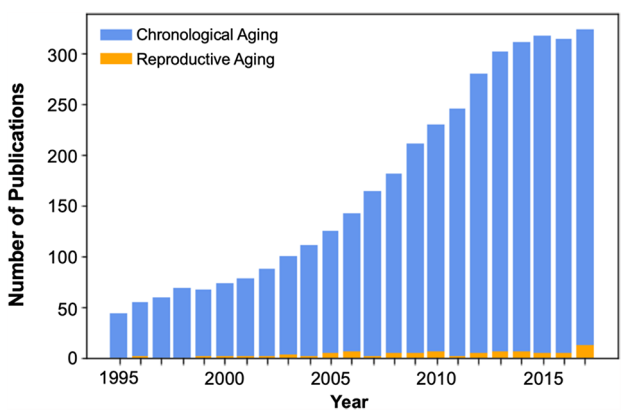

FIGURE 1 | Publication count of cognitive neuroscience studies of aging, beginning in the mid-1990s with the widespread adoption of functional brain imaging techniques. The number of brain imaging publications that consider the effects of reproductive or "neuroendocrine" aging during the midlife transition to menopause is dwarfed by the number of chronological aging studies, which compare men and women >65 to young adults. Over the past 23 years there have been only 82 brain imaging publications on reproductive aging. Of those, only 49% used endocrine assessments to verify menopausal stage (see **Supplementary Material**).

Estradiol signaling is a critical component of cell survival and plasticity, and its effects can be measured across multiple spatial and temporal scales (Frick et al., 2018). Many of these effects occur in brain regions that are critical to higher level cognitive function and cognitive aging. In non-human primates, at the cellular level, nearly 50% of prefrontal cortex (PFC) pyramidal neurons express the ERα subtype (Wang et al., 2010), and greater ERα expression is associated with better short-term memory performance (Wang et al., 2010). Further, the suppression of ovarian hormones decreases spine density in PFC neurons (Hao et al., 2006), and impairs working memory performance (Rapp et al., 2003). In rodents, in the hippocampus, dendritic spine density in CA1 neurons varies over the course of the estrous cycle (Woolley et al., 1990; Woolley and McEwen, 1993). At the macroscopic level, hippocampal volume is regulated by sex hormones (Galea et al., 1999) and fluctuates across the estrous cycle (Qiu et al., 2013). These basic science findings provide converging evidence that the manipulation of estrogen levels leads to structural and functional changes in the ER-enriched regions that comprise memory circuitry.

Human studies further implicate sex steroids in the regulation of memory circuitry (Berman et al., 1997; Shaywitz et al., 1999; Jacobs and D'Esposito, 2011; Epperson et al., 2012; Hampson and Morley, 2013; Shanmugan and Epperson, 2014; Jacobs et al., 2015, 2016, 2017; Albert et al., 2017; Girard et al., 2017; Zeydan et al., 2019), yet despite this evidence the neuroendocrine basis of cognitive aging remains understudied in human neuroscience.

MENOPAUSE AND HORMONE THERAPY

One of the most significant neuroendocrine changes in a woman's life is the transition to menopause, during which circulating ovarian hormone concentrations decline up to 90%. Many women report changes in memory and attention (e.g., "menopause fog") during this transitional period (Greendale et al., 2011). The median age of menopause is 52.4 years (Gold et al., 2001), yet the vast majority of cognitive aging studies target adults age 65 and older, missing this critical midlife window (**Figure 1**). The field has focused almost exclusively on the neural and cognitive effects of chronological aging, overlooking the impact of reproductive aging. This is striking, given that most women will spend one-third of their lives in the post-reproductive years, and mounting evidence suggests that reproductive aging influences brain structure, function, and cognition.

A significant methodological and ethical challenge of studying menopause is that to fully understand the impacts of this major hormonal shift on the brain, our designs must parse the parallel and interactional effects of chronological and reproductive aging in women. In humans, the relationship between gonadal aging and the brain has typically been studied in two contexts: studying the effects of spontaneous menopause and surgical menopause (e.g., bilateral salpingo-oophorectomy prior to natural menopause). For longitudinal studies of women experiencing spontaneous menopause, the effects of chronological and reproductive aging cannot be separated. However, in studying women who have undergone surgical menopause or cross-sectional studies that pair age-matched women who fall within different stages of the menopausal transition, the effects of reproductive aging alone can be more effectively characterized.

Impact of Gonadectomy and Hormone Supplementation in Animals

While challenging in humans, animal studies more easily decouple the effects of reproductive aging from chronological aging *via* surgical menopause (gonadectomy) paradigms. These studies demonstrate that ovarian hormone depletion impacts hippocampal and PFC morphology and function, independent of the established influence of chronological aging. This body of work has made significant progress toward characterizing the synaptic basis of menopause-related memory decline (Morrison and Baxter, 2012; Hara et al., 2016). For example, rodent and nonhuman primate studies first identified estradiol's role in modulating structural plasticity in the hippocampus and PFC as well as estradiol's protective effects against cognitive decline (Morrison and Baxter, 2012; Hara et al., 2015, 2016). In female macaques, surgical menopause leads to a 30% loss in spine density in hippocampal CA1 neurons, which is reversed by estradiol replacement (Dumitriu et al., 2010). Natural menopause in rhesus monkeys reduces the density of perforated synapse spines in CA1 neurons, which is correlated with lower recognition memory (Hara et al., 2012). Cyclic estradiol administration in postmenopausal female monkeys restores dorsolateral PFC spine density and the frequency of multisynaptic boutons to levels comparable to premenopausal females, and these synaptic-level changes are accompanied by enhanced performance on PFC-dependent memory tasks in estradiol-treated animals (Hara et al., 2016; Kohama et al., 2016).

Impact of Menopause and Hormone Supplementation in Humans

Epidemiological surveys indicate that many women report increased forgetfulness and "brain fog" during the menopausal transition (Greendale et al., 2011). Neuropsychological studies have identified decrements in verbal fluency and associative memory tied to reproductive stage (Epperson et al., 2013; Weber et al., 2014; Rentz et al., 2017), and across women higher estradiol levels are associated with better memory performance (Rentz et al., 2017).

At the level of functional brain networks, our group showed that PFC activity and working memory performance are modulated by endogenous estradiol concentrations (Jacobs and D'Esposito, 2011; Jacobs et al., 2017). Using a within-woman, repeated-measures approach that capitalizes on the natural fluctuations in estradiol over the menstrual cycle in premenopausal women, we found that PFC activity is exaggerated when estradiol concentrations are low, a putative marker of neural inefficiency (Jacobs and D'Esposito, 2011). This "inefficient" PFC response is also evident in midlife

women as ovarian estradiol production declines during the menopausal transition (Jacobs et al., 2016). In another population-based functional magnetic resonance imaging (fMRI) study, midlife men and women (N = 200; age range: 45–55) performed a verbal memory encoding task. Task-evoked hippocampal responses differed by women's reproductive stage, despite minimal difference in chronological age. Across women, lower estradiol concentrations were related to greater alterations of hippocampal connectivity and poorer performance on a subsequent memory retrieval task, implicating sex steroids in the regulation of memory circuitry (Jacobs et al., 2016, 2017). Thus, early functional changes in memory circuitry are evident decades before the age-range typically targeted by cognitive neuroscience studies of the aging brain.

At the level of brain morphology, Zeydan et al. (2019) found that abrupt hormonal changes associated with early surgical menopause lead to structural abnormalities in the medial temporal lobe. The parahippocampus-entorhinal cortex was thinner in women who underwent bilateral ovariectomization compared to an age-matched premenopausal control group, despite the use of estrogen replacement in the surgical menopause group. Future studies should employ high resolution hippocampal subfield imaging to identify the impact of hormone suppression within specific medial temporal lobe structures, particularly subfields that may differ by cytoarchitecture and magnitude of ERα- and ERβ-expression.

A handful of human studies have directly examined the effect of hormone therapy (HT) on brain morphology in peri/postmenopausal women, revealing that hippocampal volume increases in response to certain hormone replacement regimens (Albert et al., 2017). The macrostructural changes evident in the hippocampus in response to estradiol supplementation may produce cognitive benefits (for a review, see Daniel et al., 2015). For example, Maki et al. (2011) found that women who began HT in perimenopause had enhanced hippocampal activity during a verbal recognition task and better verbal memory performance relative to nonusers. When initiated early in the menopausal transition, HT also appears to enhance cognitive control-related dorsolateral PFC activity and improve task-switching performance in women (Girard et al., 2017).

Together, these findings underscore the importance of considering reproductive stage, not simply chronological age, to identify neural and cognitive changes that unfold in the middle decade of life. In keeping with animal evidence, human studies demonstrate that the decline in ovarian estradiol production during menopause plays a role in shaping the structure and function of brain networks that support higher-order cognitive functions.

PREGNANCY

With a global fertility rate of 2.5 births per woman (World Bank, 2017), the majority of women will experience pregnancy at least once in their lifetime. Pregnancy is another prolonged period of major hormonal change, during which women experience a dramatic rise in sex steroid hormone concentrations. For instance, in humans, estradiol and progesterone levels increase up to 300-fold across the 40-week gestational period (Berg and Kuss, 1992; Tal et al., 2000; Schock et al., 2016), with progesterone levels rising from a mean of 1 ng/mL during an average menstrual cycle to 100–300 ng/mL during the last trimester of pregnancy (Tal et al., 2000; Schock et al., 2016). In rodents, this sustained increase in hormone levels during gestation has a lasting impact on the brain, particularly regarding hippocampal plasticity (reviewed in Kinsley and Lambert, 2008; Workman et al., 2012; Galea et al., 2014).

Impact of Pregnancy on Brain Structure/Function in Animals

In rodents, the reproductive experience (i.e., pregnancy, lactation, and parenting) affects hippocampal morphology (Kinsley et al., 2006; Pawluski and Galea, 2006, 2007; Barha et al., 2015). Hippocampal CA1 spine density is significantly higher in late pregnancy and lactating females compared to nulliparous female rats at any phase of the estrous cycle (Kinsley et al., 2006). Pregnancy also affects long-term hippocampal sensitivity to estrogen (Roes and Galea, 2016). Barha and Galea (2011) studied hippocampal sensitivity to estrogens (17β, 17α, and estrone) in middle-aged rats as a function of parity (multiparous vs. nulliparous). All estrogens induced upregulation of cell proliferation in the hippocampus in multiparous females, however, none of the estrogens induced proliferation in nulliparous females. Further, pregnancy's effects appear to be cumulative, such that the effects of pregnancy compound with subsequent parity. In a study of spatial learning and memory, Gatewood et al. (2005) found that multiparous rats exhibited better spatial learning and memory retention compared to age-matched primi- and nulliparous females when tested at 6, 12, 18, and 24 months of age. Additionally, immunohistochemistry within the CA1 region and dentate gyrus of the hippocampus of these rats revealed an effect of reproductive experience on amyloid precursor protein (APP) immunoreactive neurons. Multiparous females had fewer APP stained cells than primi- and nulliparous groups, and less APP staining corresponded with better behavioral performance at 24 months.

Impact of Pregnancy on Brain Structure/Function in Humans

Pregnancy typically confers an enhancement of hippocampal-dependent memory in rodents, yet human studies report memory impairments during pregnancy. Similar to the self-reported cognitive changes experienced by menopausal women, pregnant women describe cognitive changes during pregnancy that include increased forgetfulness, greater distractibility, and word finding difficulties (reviewed in Brett and Baxendale, 2001). In a meta-analysis, Henry and Rendell (2007) observed that pregnant women exhibit impairments in free and delayed recall, subjective memory (persisting 3 months post-partum), and working memory relative to non-pregnant controls. Pregnant women did not outperform non-pregnant women in any domain. Glynn (2012) found that the effects on memory are cumulative with increasing

parity. In the study, 254 women were evaluated on measures of verbal recall memory at four points during pregnancy and at 3 months post-partum. Beginning at 16 weeks' gestation, the performance of women who had given birth more than twice was worse than the performance of women who had given birth once, which was worse than women who had not yet given birth (primigravid), with impairments persisting to 3 months post-partum.

Few neuroimaging studies have been conducted during pregnancy in humans. Limited findings suggest that global brain volume decreases during pregnancy (Oatridge et al., 2002) with an increase in brain volume after delivery (Kim et al., 2010), returning to pre-pregnancy levels by 24 weeks post-partum (Oatridge et al., 2002). Hoekzema et al. (2017) observed gray matter volume (GMV) reductions in primiparous women scanned before and after pregnancy. Reductions were observed across a network of regions that support social cognition and theory of mind, including the hippocampus, precuneus, and medial/inferior frontal gyrus. Gray matter volume reductions persisted up to 2 years post-partum (with some rebound in the hippocampus). The authors propose that these gray matter changes may facilitate the transition to motherhood, as the areas exhibiting volumetric reductions also exhibited the strongest fMRI BOLD response to pictures of the mothers' infants compared to unrelated children. The magnitude of the morphological change (e.g., in cortical thickness, surface area, sulcal depth, etc.) in these mothers as a result of pregnancy were on par with the changes observed in adolescent males and females during the pubertal transition (Carmona et al., 2019).

Association Between Pregnancy and Cognitive Aging

Greater lifetime exposure to estrogen is considered to be neuroprotective (Smith et al., 1999; Rasgon et al., 2005; Ryan et al., 2009; Heys et al., 2011; Tierney et al., 2013) and pregnancy has a lasting impact on circulating sex steroid hormones. Pregnancy appears to reduce lifetime estrogen exposure relative to nulliparity (summarized in Smith et al., 1999). Circulating estrogen levels are ∼22% lower in parous women compared to nulliparous women (Bernstein et al., 1985). This difference persists through menopause, with 20% lower free estradiol levels in multiparous (≥4 children) compared to primiparous menopausal women (Chubak et al., 2004). This parity-related difference in hormone levels may contribute to findings that lower parity is associated with better postmenopausal cognitive function (McLay et al., 2003; Heys et al., 2011; but see Ryan et al., 2009; Tierney et al., 2013). Similarly, parity may have an effect on cognitive aging and dementia risk (reviewed in Roes and Galea, 2016), with reports that having children correlates with earlier onset of AD (Ptok et al., 2002) and a greater extent of AD pathology post-mortem (Beeri et al., 2009). Some of these effects are compounded by successive pregnancies (Sobow and Kloszewska, 2004; Colucci et al., 2006).

ORAL HORMONAL CONTRACEPTIVE USE

Ten million women in the US and 100 million women worldwide use oral hormonal contraception (OC; Petitti, 2003; Christin-Maitre, 2013; Jones et al., 2013; Daniels and Mosher, 2013; Daniels et al., 2015). First introduced in the US in 1960, "the pill" revolutionized women's reproductive health. However, emerging evidence suggests that OCs influence aspects of brain structure and function in young adults (for review, see Pletzer and Kerschbaum, 2014). In two MRI studies, OC use in women was associated with increased GMV in the amygdala, parahippocampal gyrus (Pletzer et al., 2010; Lisofsky et al., 2016) and ventral temporal cortex (Pletzer et al., 2010, 2015) relative to non-users. Less robust effects have been observed in the PFC, although this finding is inconsistent across studies (Pletzer et al., 2010; De Bondt et al., 2013b; Petersen et al., 2015). Moving forward, the field would benefit from a well-powered study that can determine the influence of OC formulation, age of initiation, and duration of use on global and regional brain morphology.

No systematic study has been conducted to investigate the effects of chronic ovarian hormone suppression on brain regions that are densely populated with sex steroid receptors and are modulated by sex steroid hormones. Does long-term ovarian hormone suppression have consequences at the macroscopic level of regional brain morphology in humans? Are there enduring effects even after cessation of use? Though this area of research is understudied, retrospective studies suggest that OC use confers a positive effect on cognitive aging (Egan and Gleason, 2012; Karim et al., 2016). For instance, in an epidemiological study of postmenopausal women, Karim et al. (2016) found that hormonal contraceptive use was positively associated with global cognition and verbal memory. However, other studies report no relationship between OC use and cognitive outcomes (McLay et al., 2003; Tierney et al., 2013). The dearth of research on this topic is especially apparent when attempts are made to explain the endocrine basis of OC's cognitive effects, with some studies attributing positive effects to the supraphysiological levels of synthetic sex hormones in OC users (Egan and Gleason, 2012; Karim et al., 2016), while other studies refer to suppressed levels of endogenous estrogen in OC users (Griksiene and Ruksenas, 2011; De Bondt et al., 2013a). Careful endocrine evaluations paired with studies that control for OC formulation are necessary to resolve these discrepancies.

In addition to OC formulation, the age of initiation of OC use must be considered. Up to one-third of OC users begin to use in early adolescence, yet we know relatively little about how hormone suppression impacts the developing brain, and this may be critical for understanding OC's effects throughout the lifespan. While the hippocampus and basal ganglia typically reach adult levels in late childhood or early adolescence (Segawa, 2000; Gogtay et al., 2006), the development of the PFC is protracted, with cortical volumes stabilizing in the mid-20s (Lenroot and Giedd, 2006). The neuroendocrine changes that accompany puberty produce what has been referred to as a second "window of opportunity" or sensitive period in brain development (for review, see Fuhrmann et al., 2015). In females, the pubertal transition typically begins at

10–11 years of age and ends between the ages of 15–17. It is during this pubertal period that many women begin OC use. Among insured teenagers in the United States, 6% of 13-year-olds and 36% of 13–18-year-olds filled a prescription for OC in 2009 (Ehrlich et al., 2011). Given the early age of first exposure, OC use has the potential to alter the organizational effects of endogenous estradiol in adolescents through chronic suppression of sex steroid hormone levels. To our knowledge, no large-scale longitudinal study has examined the impact that age of initiation and duration of OC use have on neuronal development. Additionally, the short- and long-term effects of OC likely differ. In adults, short-term OC use is associated with GMV changes (Pletzer et al., 2015; Lisofsky et al., 2016), yet few studies have examined whether these changes persist over time, or whether the magnitude of GMV change correlates with total duration of use (Pletzer et al., 2010; De Bondt et al., 2013b; Petersen et al., 2015).

ADDRESSING THE UNDER-REPRESENTATION OF WOMEN'S HEALTH FACTORS IN FUTURE AGING STUDIES

The biomedical sciences are witnessing a remarkable change, whereby researchers are recognizing the importance that sex plays in virtually all aspects of health and disease (Cahill, 2006; McCarthy, 2008). However, in neuroscience, the influence of biological sex and sex hormones on the aging brain remains understudied, leaving a critical gap in our understanding of the aging process. Researchers in the cognitive aging field often account for a variety of "lifespan" factors when characterizing their sample population (e.g., years of education, lifetime physical activity, history of smoking, or substance abuse), yet the endocrine lifespan is usually overlooked.

Recently there has been an appeal for earlier identification of individuals at risk for cognitive decline and dementia, with increasing focus on middle age. Yet few human studies have investigated the neurobiological and neuropsychological impact of reproductive aging, the onset of which coincides with this critical midlife window. Moving forward, the field should pay greater attention to the endocrine basis of brain aging by targeting under-represented samples of women, such as midlife women transitioning through menopause, women undergoing chronic hormone suppression for endocrine-related disorders like endometriosis, and women who undergo early surgical menopause. Enriching this area of research is sorely needed.

In addition to designing studies that address the needs of under-served populations, researchers can take a simpler step forward by adding a standardized reproductive health history questionnaire to their demographic batteries. This is particularly important for large-scale, publicly available data repositories that collect brain imaging and cognitive data on community-based cohorts (e.g., WU-Minn Human Connectome Project, Harvard Brain Genomics Superstruct Project, Philadelphia Neurodevelopmental Cohort). Few of these databases include standardized data on parity, use of hormone-based medications, menstrual cycle histories and/or incidence of common endocrine disorders. The Human Connectome Project-Aging makes progress on this front by collecting serum and saliva samples for hormone characterization and by using an enriched medical history questionnaire that includes some assessments of reproductive health (Bookheimer et al., 2019).

If the practice of collecting a standardized reproductive health history becomes routine, the field will be better able to incorporate hormone factors into models of the aging brain and can then use these findings to guide tightly controlled follow-up studies. Adopting this standard would provide a richer characterization of the sample population being studied and could enable meta-analyses that model the impact of endocrine variables on brain and cognitive outcomes. For example, do women who undergo early vs. late menopause show worse cognitive performance and greater neuropathology later in life? Does age of initiation or duration of OC use alter age-related changes in brain morphology? Do common medications that suppress sex hormone levels (e.g., Lupron for endometriosis) have enduring effects on brain structure, function, and cognition? Answers to these questions are long overdue.

CONCLUSION

The biomedical sciences have treated the male as the representative sex for half a century. As Kathleen Okruhlik wrote in Okruhlik (1994):

> *"...the treatment of menstruation, pregnancy, and childbirth as diseases or medical emergencies may be traced to the fact that these are not things that happen to the ideal healthy human being who is, of course, male. The ideal healthy lab rat is also male. His body, his hormones, and his behaviors define the norm; so he is used in experiments. Female hormones and their effects are just nuisance variables that muck up the works, preventing experimenters from getting at the pure, clean, stripped-down essence of rat-hood as instantiated by the male model. Insofar as the female of the species is truly a rat (or truly a human being), she is covered by the research on males. Insofar as she is not included in that research, it is because she is not an archetypal member of her own species. The dangerous effects of such research procedures, especially in the biomedical sciences, are just now being documented. For far too long, the assumption underlying these experimental designs (that males are the norm) simply went unchallenged."*

Science has to represent society, especially since the bulk of academic research is publicly funded by tax-payer dollars. Moving forward, scientists must ensure that our research program serves men and women alike. Historically, cognitive neuroscience has largely overlooked aspects of the human condition (the menstrual cycle, OCs, pregnancy, menopause) that are relevant to half of the world's population (and half of the US tax-base), and should correct course in order for the field to advance.

DATA AVAILABILITY

No datasets were generated or analyzed for this study.

AUTHOR CONTRIBUTIONS

CT, LP and EJ wrote the manuscript. LP and SY edited the manuscript. SY conducted the literature survey provided in the supplemental figures.

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SUPPLEMENTARY MATERIAL

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Origins Matter: Culture Impacts Cognitive Testing in Parkinson's Disease

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Cognitive decline is common in Parkinson's disease (PD), and precise cognitive assessment is important for diagnosis, prognosis, and treatment. To date, there are no studies in PD investigating cultural bias on neuropsychological tests. Clinical practice in multicultural societies such as, Toronto Canada where nearly half of the population is comprised of first generation immigrants, presents important challenges as most neuropsychological tools were developed in Anglosphere cultures (e.g., USA, UK) and normed in more homogeneous groups. We examine total scores and rates of deficits on tests of visuoperceptual/visuospatial, attention, memory, and executive functions in Canadians with PD born in Anglosphere countries (n = 248) vs. in Canadians with PD born in other regions (International group; n = 167). The International group shows lower scores and greater rates of deficits on all visuoperceptual and some executive function tasks, but not on attention or memory measures. These biases are not explained by demographic and clinical variables as groups were comparable. Age at immigration, years in Canada, and English proficiency also do not account for the observed biases. In contrast, group differences are strongly mediated by the Historical Index of Human Development of the participants' country of birth, which reflects economic, health, and educational potential of a country at the time of birth. In sum, our findings demonstrate lasting biases on neuropsychological tests despite significant exposure to, and participation in, Canadian culture. These biases are most striking on visuoperceptual measures and non-verbal executive tasks which many clinicians still considered to be "culture-fair" despite the growing evidence from the field of cross-cultural neuropsychology to the contrary. Our findings also illustrate that socio-development context captures important aspects of culture that relate to cognition, and have important implications for clinical practice.

Keywords: neuropsychology, visuospatial, executive function, memory, cultural bias, human development index, mild cognitive impairment

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INTRODUCTION

While basic cognitive processes are often considered universal (Nell, 1999), clinical neuropsychologists and cognitive neuroscientists recognize that a person's culture impacts how these processes are expressed in behavior such as in their performance on neuropsychological tests (for review, see Puente and Agranovich, 2003; Rivera Mindt et al., 2010; Fernández and Abe, 2018).

Because culture also influences the design of cognitive tests (Cole, 1998), it is not surprising that people born and raised where tests are conceived have an advantage. Indeed, what constitutes an average score for well-known cognitive tests (for example the Wechsler scales) varies considerably across different regions of the world. Most tests are developed, standardized, and normed in the United States of America (USA) and United Kingdom (UK), and these two countries are not only predominantly English-speaking, but also share cultural and historical roots and similar high levels of economic and social development. These similarities also extend to other "Anglosphere" countries (a term we borrow from the writer Neal Stephenson), such as Canada, Australia and New Zealand. Cultural biases on cognitive testing are not only evident between disparate geographical regions, but also arise within multicultural societies. However, most of this research has been conducted in the USA and focused on differences between racial and ethnic groups, which is confounded by other group differences such as educational attainment, literacy, English proficiency, and socioeconomic status (Chin et al., 2012; Cagigas and Manly, 2014; Krch et al., 2015; Flores et al., 2017; Weuve et al., 2018). While such research is important, it may not generalize to first-generation immigrants living in multicultural societies as new immigrants face several unique issues which do not necessarily reflect the above confounds (for review, see Ferraro, 2016).

To address cultural biases on cognitive testing, strategies have included collecting normative data for specific groups or countries and adapting existing tests. While a worthwhile endeavor, these strategies do not resolve the challenges of assessing cognition in immigrants at different stages of acculturation. It is not feasible to develop normative data for all subgroups of individuals (Shuttleworth-Edwards, 2016), especially since cultural context is dynamic and transforms from contacts with other cultures and from particular social, historical, and political contexts (Whaley and Davis, 2007). Another strategy is to identify or develop tests that are "culture-fair," but many efforts have focused on merely avoiding verbal tasks which have proven unsuccessful in eliminating cultural bias (Marcinkowska and Sitek, 2017; Fernández and Abe, 2018). We argue that prior to developing new instruments for use in multicultural settings, we must investigate the degree of bias on existing tasks as it may vary across instruments and cognitive domains, and identify associated features and sources of this bias.

In many ways, Toronto Canada is an ideal location to investigate multicultural bias given that 49% of Torontonians are first-generation immigrants born outside Canada, and 45% identify some language other than English as their mother tongue (Statistics Canada, 2017). Moreover, 50% of Toronto's immigrants entered the country under the "economic" status meaning that they are generally well-educated and were granted entry into Canada due to their ability to contribute to the Canadian economy [e.g., occupation meets labor market needs, ability to own a business, ability to make substantial investments (Statistics Canada, 2017)]. Immigrants to Canada are also healthier than Canadian-born individuals based on rates of mortality (Ng, 2011) and of chronic conditions such as diabetes and cardiovascular conditions (Newbold and Filice, 2006). These last facts are important because they address some of the criticisms of cross-cultural neuropsychological research in the USA where race/culture is highly confounded with socioeconomic status, educational inequality and health (Rosselli and Ardila, 2003; Schwartz et al., 2004; Chin et al., 2012; Krch et al., 2015; Ferraro, 2016; Weuve et al., 2018).

In the present study, we examine cultural bias in advanced Parkinson's disease (PD). While this patient group was selected for convenience given the availability of a rich neuropsychological dataset at our center, such investigation is particularly relevant in this patient group where cognitive decline is very common (Emre et al., 2007; Litvan et al., 2012), and the presence of severe cognitive impairment or dementia may preclude access to advanced therapies such as deep brain stimulation (DBS; Lang et al., 2006). As such, if testing is biased, it has the potential to result in health and treatment access inequities. To our knowledge, the effect of cultural diversity has not yet been investigated in this clinical group. In a large cohort of PD patients, we examine whether the frequency of cognitive diagnoses (PD mild cognitive impairment and dementia) differ between people born in Anglosphere countries (Canada, USA, UK), where tests are predominantly developed and normed, relative to individuals born outside these countries (International group), based on clinical interviews and comprehensive neuropsychological testing. On a subset of 12 neuropsychological tests from these assessments, we examine whether the Anglosphere group has higher performance/lower rates of deficits relative to the International group. These tests sample four cognitive domains, namely attention, memory, visuoperceptual/visuospatial skills, and executive functioning. To identify potential sources of bias, we first compare groups' demographic (i.e., age, sex), socio-economic status (i.e., education, occupational attainment) and clinical characteristics (i.e., disease severity). These demographic and disease-related variables are examined to ensure that the groups are comparable on variables known to impact cognition (e.g., older age, severe PD, and lower education are associated with poorer cognition) so that any between-group differences can be more confidently attributed to sociocultural factors. On biased tasks only, we then investigate whether performance in the International group is associated with immigration variables (e.g., years in Canada, age at immigration) and coarse measures of English proficiency (e.g., English as a mother-tongue, use of interpreter). Last, we investigate whether the relationship between group membership (Anglosphere vs. International) and cognitive performance is mediated by socio-development levels of countries of origin as measured using the Historical Index of Human Development (HIHD; Prados de la Escosura, 2015). The HIHD is an extension of the United Nations Human Development Index (UN-HDI; United Nations Development Programme, 1990) that includes data corresponding to our participants' country and year of birth. It evaluates countries' development and well-being beyond economic growth alone, in a scalable and multidimensional manner. Although it does not reflect all aspects of culture, it captures societal factors that facilitate an individual's growth as

it represents people's ability to access resources (i.e., longevity, education, standard of living).

MATERIALS AND METHODS

Participants

With approval from the research ethics board of the University Health Network (UHN), we conducted a retrospective chart review of advanced PD patients evaluated to determine their candidacy for DBS surgery at Toronto Western Hospital UHN between September 2014 and December 2018. Their multidisciplinary evaluation included a comprehensive neuropsychological assessment and a neurological assessment. Clinical neuropsychologists (M.C. or M.S.) supervised all psychometric testing, conducted clinical interviews, and assigned cognitive diagnoses. The motor examinations were completed by Movement Disorders neurologists. After excluding 40 of the 455 consecutive patients assessed due to other neurological conditions (e.g., prior stroke, TBI with loss of consciousness, epilepsy, prior neurosurgical intervention) or due to incomplete neuropsychological assessments (i.e., missing more than three of the neuropsychological tests of interest), a total of 415 patients were included. Of these, 248 are individuals born in Canada, the USA, and the UK (Anglosphere group), and 167 were born outside these countries (International group). Most participants in the latter group were born in Asia (55%), followed by Europe (23%), the Americas/Caribbean (14%), and Africa (7%), and none were born in Oceania. These proportions are consistent with the general immigrant population of the Toronto Census Metropolitan Area (Statistics Canada, 2017). The number of participants per specific country and world region is presented in **Supplementary Table S1**.

Socio-demographic and Disease-Related Variables

Socio-demographic variables include current age, sex, years of formal education, and highest occupation category based on the International Standard Classification of Occupations (International Labour Office, 2012), which includes: (1) managers; (2) professionals; (3) technicians, associate professionals, and clerical workers; (4) craft and trades; (5) services and sales workers; and (6) operators, assemblers, and elementary occupations. Some of the ISCO-08 categories are combined for office workers (technicians and associate professionals class combined with clerical workers) and factory workers (operators and assemblers class combined with elementary occupations), as some positions can be assigned to different categories based on the occupation responsibilities and level of specialization required and this level of detail was not available. If multiple occupations were reported for an individual, the more specialized occupation was coded irrespective of the country in which it was performed. Variables of disease severity include disease duration (years), levodopa equivalence daily dose (LEDD; Tomlinson et al., 2010), motor scores on the Unified Parkinson's Disease Rating Scale part 3 (UPDRS part 3; Fahn and Elton, 1987). ON and OFF medications, and % levodopa response [(UPDRS part 3 ON—UPDRS part 3 OFF)/UPDRS part 3 OFF]. Some participants ($n = 57$) were evaluated using the new Movement Disorders Society (MDS)-UPDRS part 3 (Goetz et al., 2008), and their scores were transformed to be equivalent to the older version (−7 pts or score of 0 if negative; Hentz et al., 2015). Of note, greater disease severity is reflected by high scores on the UPDRS part 3, high LEDD, and longer disease duration. Additional disease-related variables relate to cognitive diagnoses in PD. Specifically, M.C. and M.S. applied the MDS diagnostic criteria for PD Mild Cognitive Impairment (PD-MCI; Litvan et al., 2012) and PD Dementia (PDD; Emre et al., 2007) based on participants' full neuropsychological assessment. PD-MCI diagnosis requires self- or family-report of progressive cognitive decline but preserved independence with daily life function, and poor performance (i.e., 1.5 SD below normative mean) on at least two neuropsychological tests. In contrast, PDD requires impairments in at least two domains of cognition, and loss of daily functioning due to cognitive decline.

Neuropsychological Measures

Although the neuropsychological test battery varied across patients, we selected a subset of measures administered that were common to most assessments and sampled visuoperceptual/visuospatial skills, attention, memory, and executive functioning. Core language skills such as naming and vocabulary are not included as they are not consistently assessed in the International group due to variable language proficiency and well-known cultural bias. Although we recognize that cognitive tasks can tap multiple cognitive domains, we list them here according to their typical classification in clinical neuropsychology. Visuoperceptual/visuospatial measures include the item-response theory version of the Benton Judgement of Line Orientation (JLO; Benton et al., 1983; Spencer et al., 2013), Object Decision and Silhouettes subtests of the Visual Object and Space Perception battery (VOSP; Warrington and James, 1991), and the copy of Rey-Osterrieth Complex Figure (ROCF; Meyers and Meyers, 1995). *Attention* was assessed using the Digit Span subtest of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III; Wechsler, 1997). *Memory* measures include Total Recall (immediate recall of trials 1–5) and Long Delay Free Recall (LDFR) on the California Verbal Learning Test 2nd edition (CVLT-II; Delis et al., 2000), as well as Recognition on the ROCF (Meyers and Meyers, 1995). We selected the ROCF Recognition over the ROCF free recall trials for our analyses as it has no motor or visuoconstruction component, and as such, provides a purer memory measure. *Executive functioning* measures include errors on the Conditional Associative Learning Test (CALT; Taylor et al., 1990), Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence 2nd edition (WASI-II; Wechsler, 2011), Category Fluency (Animals and Boys Names) from the Delis Kaplan Executive Function System (DKEFS; Delis et al., 2001), and errors on the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993). Administration of the WCST was discontinued for 55 individuals who achieved zero categories at the midpoint (64 cards) as per administration rules, and their number of errors was doubled to be comparable to scores of individuals who completed the full test. Of these

tasks, four measures involve verbal material (Digit Span, Category Fluency, and CVLT-II Total Recall and LDFR). For each measure, we derived two key variables: (1) the total raw scores; and (2) the frequency of impairment defined as scores falling at or below 1.5SD or 6th cumulative percentile relative to age-education corrected normative data for the ROCF and WCST errors [full version (Heaton et al., 1993) or WCST 64 norms for 55 individuals (Kongs et al., 2000)], and relative to age-corrected normative data for the remaining tests.

Societal and Immigration Variables

For the International group, immigration variables include age at immigration and years in Canada. As coarse measures of English proficiency, mother-tongue (includes English or not), and whether the neuropsychological assessment was completed with the assistance of a professional interpreter were also coded. The option of completing the assessment with an interpreter is offered to all patients who did not complete any part of their schooling in English. Typically, interpretation services were provided in situations wherein individuals have limited or no English proficiency, or when requested by patients. The degree of assistance varies; interpreters may provide clarifications only, adapt and administer tasks with verbal materials in the individual's preferred language (e.g., Digit Span, CVLT-II, Category Fluency), or provide complete translation of all test instructions and test materials.

For participants in both the Anglosphere and International group, a socio-development context variable is assigned, namely the Historical Index of Human Development (HIHD; Prados de la Escosura, 2015). The HIHD is a historical extension of the United Nation Human Development Index (UN-HDI;United Nations Development Programme, 1990) which is a summary measure of average achievement in key dimensions of human development including health (life expectancy), education (literacy and school enrollment) and standard of living (gross domestic product *per capita* at purchasing power parity). The HIHD value is a number between 0 and 1 with the highest scores representing higher achievement on these combined dimensions. An HIHD score is obtained for each individual based on their country of birth at their year of birth. HIHD values are not available during World War II (WWII). Therefore, any individual born between 1938 and 1944 was assigned their country's 1938 HIHD value (n = 33; 27 Anglosphere, 6 International). Any individual born between January 1945 and June 1952 (post-WWII) was assigned their country's 1950 HIHD value (n = 144; 93 Anglosphere, 51 International). From 1950 onwards, HIHD data is available in 5-year intervals (i.e., 1950, 1955, 1960, etc.). Individuals born 2.5 years before or 2.5 years after a given year were assigned their country's value for that year (e.g., born between July 1957 and June 1962, assigned value from 1960).

STATISTICAL ANALYSES

All analyses were performed using SPSS v. 22. Differences between the Anglosphere and the International groups were assessed with the non-parametric, Mann-Whitney U test based on ranks for demographic variables, disease-related variables, neuropsychological test raw scores, and societal variables. This non-parametric test was selected because some variables were not normally distributed. We used chi-square to compare groups' frequency of impaired neuropsychological test scores. Analyses of the performance on the 12 neuropsychological measures were corrected for multiple comparisons using Bonferroni ($p < 0.004$ or $p < 0.05$ corrected for 12 comparisons). Significance level was uncorrected ($p < 0.05$) for analyses of group demographic and disease-related variables.

For measures showing a significant difference between the Anglosphere and the International groups on both the total score and the frequency of impairment, we carried out further analyses to identify related features and sources of this bias. First, we examined whether age at immigration and years in Canada are related to total score performance in the International group only using Spearman correlations corrected for multiple comparisons ($p < 0.002$ or $p < 0.05$ corrected for 12 comparisons). Second, we investigated the contribution of English proficiency by comparing the total score performance between participants in the International group based on whether English is a mother-tongue, and whether they were tested with or without an interpreter using Mann-Whitney U corrected for multiple comparisons ($p < 0.008$ or $p < 0.05$ corrected for six comparisons). For the latter analyses, in cases where significant difference are noted, we also verified whether these remained after controlling for demographic variables that differed between subgroups.

Third, we investigated whether the relationships between group (Anglosphere vs. International) and performance are mediated by socio-development context (HIHD). Mediations analyses were selected because HIHD and group membership are collinear (VIF > 5), and hence, not appropriate for multiple regression models. We used PROCESS v.3.3[1] (Hayes, 2017) implemented in SPSS to test our mediation models. We used bootstrapping (5,000 resampling) with 95% confidence intervals to test whether the mediated models are significantly different from the direct models. Any confidence interval that did not include 0 was considered significant. Because the WCST errors showed a bimodal distribution of residuals, this variable was not analyzed further using mediation models.

RESULTS

Demographic and Clinical Characteristics

Socio-demographic and clinical characteristics, presented in **Table 1** with related statistics, show that the International and Anglosphere groups are comparable. Indeed, there are no significant group differences in terms of sex and years of education which is high in both groups (Md = 14 for both groups). Occupation classification was also not different between groups and demonstrates high occupational achievement in both groups with more than half having been employed as managers or professionals. Four of five disease-related measures are not significantly different between groups

[1] www.processmacro.org

TABLE 1 | Demographic, disease-related, and societal characteristics of Canadian Parkinson's disease (PD) patients based on their region of birth [Frequency and Median (IQR)].

	Anglosphere (n = 248)	International (n = 167)	Statistics (U for ranks, χ^2 for frequency)
Socio-demographic			
Age	63.55 (10.44)	61.77 (11.17)	U = 17,492, p = 0.007*, d = 0.27
Sex (%Female)	32.3%	39.5%	χ^2 = 2.31, p = 0.13, d = 0.15
Education (years)	14 (4)	14 (4)	U = 18,943.5, p = 0.14, d = 0.15
Highest Occupation (ISCO-08)[b]			$\chi^2_{(5)}$ = 2.33, p = 0.80, v = 0.08
- Managers	29.0%	25.7%	
- Professionals	29.8%	29.3%	
- Technicians, associates, clerical	21.4%	19.2%	
- Craft and trades	6.5%	7.8%	
- Services and sales	6.9%	9.0%	
- Operators, assemblers, elementary occupations	6.5%	9.0%	
Disease-related			
PD duration	9.22 (5.95)	9.87 (5.48)	U = 19,117.5, p = 0.18, d = 0.13
UPDRS part 3 OFF[a]	34 (14.5)	39 (17)	U = 16,236.5, p = 0.001*, d = 0.34
UPDRS part 3 ON	14 (12)	15 (12)	U = 18,983.5, p = 0.15, d = 0.14
% Levodopa response[a]	60 (24)	59 (24)	U = 20,180.5, p = 0.98, d = 0.00
Levodopa equivalent daily dose (LEDD)	1,327 (783)	1,373 (700)	U = 19,890, p = 0.50, d = 0.07
Cognitive complaint	86.7%	80.8%	χ^2 = 2.59, p = 0.11, d = 0.16
Psychometric	73.4%	89.8%	χ^2 = 16.84, p < 0.001*, d = 0.41 (intact vs. MCI + PDD)
Cognitive diagnosis: Intact:MCI:PDD	39.5%:60.1%:0.4%	31.7%:67.1%:1.2%	χ^2 = 2.61, p = 0.11, d = 0.16
Societal			
HIHD	0.49 (0.06)	0.23 (0.18)	U = 658, p < 0.001*, d = 2.88
Age at immigration	–	30.7 (25)	–
Years in Canada	–	27.0 (19)	–
English mother-tongue	94.8%	13.8%	χ^2 = 278.30, p < 0.001*, d = 2.85
Interpreter assistance	0.4%	32.4%	–

*Note: [a]Sample size Anglosphere = 245 and International = 165 as some individuals did not complete the UPDRS part 3 OFF medications. [b]ISCO-08, International Standard Classification of Occupations; UPDRS, Unified Parkinson's Disease Rating Scale; MCI, Mild Cognitive Impairment; PDD, Parkinson's Disease Dementia; HIHD, Historical Index of Human Development. *Significant results with p < 0.05 uncorrected.*

including the UPDRS part 3 ON, % levodopa response, LEDD, and PD duration. There are also no significant group differences in the frequency of cognitive diagnosis (combined PD-MCI and PDD vs. intact cognition) or frequency of reported cognitive complaint. However, the International group meets the psychometric criteria of the clinical cognitive diagnosis (i.e., 2 or more tests falling 1.5 SD below normative data) more frequently (16.4% difference). This confirmed that psychometric deficits are more commonly observed in the International group than in the Anglosphere group although it does not provide information on the types of deficits.

A few additional differences appear between groups. The Anglosphere group is older (1.78 years difference) and has a lower UPDRS part 3 OFF score (5 points) relative to the International group. Despite this, these variables are not used as covariates in analyses of cognitive data for simplicity and for the following specific reasons. Age is accounted for in normative scores (i.e., frequency of impairments), its potential effect on raw scores favors the International group and as such does not inflate a possible Type 1 error, and age (year of birth) is used to derive the HIHD. As for the UPDRS part 3 OFF score, this is the only disease-severity variable showing a significant difference and given that participants are tested in the ON state, it is unlikely to affect performance directly.

Neuropsychological Variables

As shown in **Table 2** and **Figure 1**, analyses yield similar finding when comparing total scores (ranks) and frequency of clinically-relevant deficits across groups. Group differences of medium to large effect sizes are observed on six measures (Cohen's d ranging from 0.30 to 0.82, see **Table 2** for statistical tests). The International group performs more poorly than the Anglosphere group on all tasks of visuoperception, including JLO, Silhouettes and Object Decision. The International group's performance is also poorer on measures of executive functioning including Matrix Reasoning, Category Fluency and WCST errors. In contrast, there is no significant group difference (Cohen's d ranging from 0.02 to 0.26) in working memory errors on the CALT, and on measures of attention and memory including Digit Span, CVLT-II Total, CVLT-II LDFR, and ROCF Recognition. There is also no significant difference in complex visuoconstruction on the ROCF copy, although a trend is observed but does not survive correction for multiple comparisons (Cohen's d of 0.20 and 0.24 for ranks and frequency of impairments, respectively).

Sources of Cultural Bias

To investigate potential contributing variables to the bias noted on measures of visuoperception and executive functioning, we first examine the relationship between the International group's total score on each biased measure and immigration variables.

TABLE 2 | Total score and frequency of impairment on neuropsychological tests in Canadian PD patients according to their region of birth.

Cognitive test	Sample size (Angl.:Intern.)	Median (IQR)		Deficit frequency		Statistics (*U* for ranks, χ^2 for frequency)
		Angl.	Intern.	Angl.	Intern.	
Attention						
Digit Span	247:166	16 (4)	15 (7)	1.2%	4.2%	U = 17,397, p = 0.009, d = 0.26 χ^2 = 3.79, p = 0.052, d = 0.19
Memory						
CVLT-II Total	248:166	42 (14)	40.5 (14)	11.3%	13.9%	U = 18,947.5, p = 0.17, d = 0.14 χ^2 = 0.61, p = 0.44, d = 0.08
CVLT-II LDFR	248:166	9 (5)	9 (6)	12.1%	18.7%	U = 20,370, p = 0.86, d = 0.02 χ^2 = 3.43, p = 0.06, d = 0.18
ROCF recognition	245:161	20 (3)	19 (3)	15.1%	19.9%	U = 18,114.5, p = 0.16, d = 0.14 χ^2 = 1.66, p = 0.21, d = 0.13
Visuoperceptual/visuospatial skills						
JLO	248:167	25 (7)	21 (8)	12.1%	35.3%	U = 13,180, $p < 0.001$*, d = 0.65 χ^2 = 31.97, $p < 0.001$*, d = 0.58
Silhouettes	247:135	21 (5)	18 (7)	7.3%	33.3%	U = 9,879, $p < 0.001$*, d = 0.72 χ^2 = 42.99, $p < 0.001$*, d = 0.71
Object Decision	248:167	17 (3)	15 (4)	16.1%	44.9%	U = 11,487.5, $p < 0.001$*, d = 0.82 χ^2 = 41.27, $p < 0.001$*, d = 0.66
ROCF copy	246:165	29 (8.5)	27 (9.5)	57.7%	69.7%	U = 17890, p = 0.041, d = 0.20 χ^2 = 6.04, p = 0.014, d = 0.24
Executive functions						
Matrix Reasoning	247:164	18 (6)	13 (10)	6.9%	25.6%	U = 14,536, $p < 0.001$*, d = 0.49 χ^2 = 28.12, $p < 0.001$*, d = 0.54
Category fluency	247:166	38 (11)	31 (11)	5.7%	18.1%	U = 11,369, $p < 0.001$*, d = 0.82 χ^2 = 16.05, $p < 0.001$*, d = 0.40
CALT errors	247:165	31 (33)	33 (39.5)	42.1%	47.9%	U = 19,353.5, p = 0.39, d = 0.09 χ^2 = 1.33, p = 0.25, d = 0.11
WCST errors	247:164	41 (40)	51 (44)	19.8%	34.1%	U = 16,725.5, p = 0.003*, d = 0.30 χ^2 = 10.61, p = 0.001*, d = 0.33

*Note: [a]CVLT-II, California Verbal Learning Test 2nd edition; LDFR, Long Delay Free Recall; ROCF, Rey-Osterrieth Complex Figure; JLO, Benton Judgement of Line Orientation; CALT, Conditional Associative Learning Test; WCST, Wisconsin Card Sorting Test. *Significant results with $p < 0.05$ corrected for multiple comparisons using Bonferroni ($p < 0.004$ corrected for 12 comparisons).*

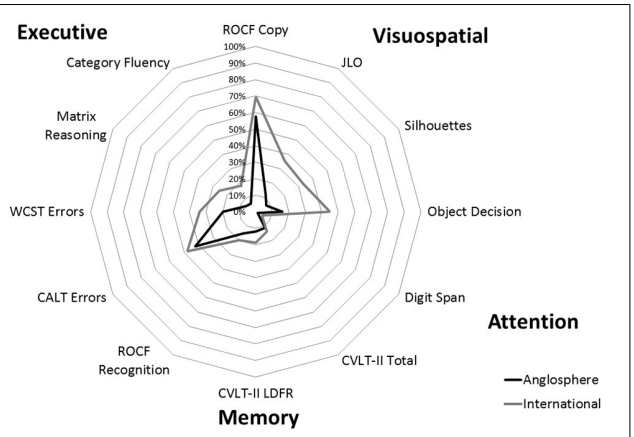

FIGURE 1 | Frequency of impairment per test across Anglosphere and International Parkinson's disease (PD) groups.

As shown in **Table 1**, the majority of the International group immigrated to Canada in adulthood (Md = 30.7, IQR = 25) and has lived in Canada for Md = 27 years (IQR = 19). We found no significant correlation ($p < 0.002$–Bonferroni corrected) between performance on the six biased measures and age at immigration (JLO: $r_s = -0.08$, $p = 0.32$; Silhouettes: $r_s = -0.14$, $p = 0.10$; Object Decision: $r_s = -0.13$, $p = 0.08$; Matrix Reasoning: $r_s = 0.03$, $p = 0.74$; Category Fluency: $r_s = -0.19$, $p = 0.01$; WCST errors: $r_s = 0.08$, $p = 0.29$) nor between performance and years in Canada (JLO: $r_s = -0.04$, $p = 0.57$; Silhouettes: $r_s = 0.02$, $p = 0.80$; Object Decision: $r_s = 0.03$, $p = 0.72$; Matrix Reasoning: $r_s = -0.16$, $p = 0.04$; Category Fluency: $r_s = 0.04$, $p = 0.64$; WCST errors: $r_s = 0.03$, $p = 0.71$).

Another potential contributing factor is participants' proficiency in English. In the Anglosphere group, English is the mother-tongue of 94.8% of participants and only a single participant was tested with an interpreter (0.4%). In contrast, in the International group, English is a mother-tongue in 13.8% of participants, and 32.4% of participants were assessed with the assistance of interpreters. However, within the International group, performance (ranks of total scores) on biased neuropsychological tasks does not differ significantly ($p < 0.008$–Bonferroni correction) between individuals for

whom English is a mother-tongue vs. those for whom it is not (JLO: U = 1,649, p = 0.97, d = 0.01; Silhouettes: U = 861, p = 0.13, d = 0.26; Object Decision: U = 1,307, p = 0.10, d = 0.25; Category Fluency: U = 1463, p = 0.40, d = 0.13; Matrix Reasoning: U = 1,425.5, p = 0.51, d = 0.10; WCST errors: U = 1280.5, p = 0.17, d = 0.21). Importantly, these analyses are quite underpowered as the sample of individuals with English as a mother-tongue is small (depending on the test, n = 19–23 report English as a mother-tongue vs. n = 116–144 report other languages).

The impact of language on performance can also be assessed by comparing the performance (ranks of total scores) of participants from the International group tested with an interpreter (n = 55) to those tested without (n = 112). Here, we demonstrate no significant difference ($p < 0.008$–Bonferroni correction) in performance on JLO (U = 2604, p = 0.10, d = 0.25), Silhouettes (U = 1559.5, p = 0.13, d = 0.26), Object Decision (U = 2486.5, p = 0.04, d = 0.31) and Category Fluency (U = 2672.5, p = 0.23, d = 0.19), but their performance is weaker on Matrix Reasoning (U = 2180.5, p = 0.006, d = 0.44) and WCST errors (U = 2075.5, p = 0.001, d = 0.52). However, whilst these two subgroups are comparable in terms of age (U = 3,003, p = 0.79, d = 0.04) and disease severity (PD duration: U = 3,045, p = 0.91, d = 0.02; UPDRS part 3 ON: U = 2647.5, p = 0.14, d = 0.23; UPDRS part 3 OFF: U = 2,995, p = 0.99, d = 0.00; % levodopa response: U = 2666.5, p = 0.30, d = 0.18; LEDD: U = 2,793, p = 0.33, d = 0.15), participants tested with interpreters have lower education than participants tested without (U = 1980.5, $p < 0.001$, d = 0.61). After regressing out years of education, group differences are reduced and below corrected statistical significance (Matrix Reasoning corrected for education: U = 2,634, p = 0.24, d = 0.18; WCST errors corrected for education: U = 2,325, p = 0.02, d = 0.37).

Because the Anglosphere and International groups were comparable on demographic and disease variables, we do not test whether these variables have a differential effect on performance on biased tasks within each group, but these data are presented in **Supplementary Tables S2, S3**. We also do not analyze differences in performance between the different world regions in the International group, but rates of impairments for each of the 12 neuropsychological measures per global region are presented in **Supplementary Figure S1** and show no striking or consistent pattern of regional bias.

Socio-development Context and Cognition

As predicted, a key difference between the Anglosphere and the International groups pertains to the HIHD which is significantly higher in the Anglosphere group (see **Table 1** for statistics). To investigate whether this socio-development context is a source of the bias observed on cognitive measures, we conducted five simple mediation analyses with group membership (x), HIHD (M), and cognitive performance on the biased tasks (Y). As noted previously, WCST errors were not analyzed in these mediation models due to its bimodal distribution of residuals. As shown in **Figure 2**, HIHD was a full mediator in four of five models and a partial mediator in one. The total effect of group membership on JLO performance was significant [c = −3.49, SE = 0.54, 95% CI (−4.55, −2.42)]. However, the direct effect of group membership on JLO was completely mediated when HIHD was taken into account [c' = −0.46, SE = 1.04, 95% CI (−2.51, 1.59)]. HIHD was also a full mediator in the relationship between group membership and Silhouettes [c = −3.08, SE = 0.41, 95% CI (−3.89, −2.27); c' = −0.72, SE = 0.78, 95% CI (−2.26, 0.82)], group membership and Matrix Reasoning [c = −2.91, SE = 0.52, 95% CI (−3.95, −1.88); c' = −0.76, SE = 1.03, 95% CI (−2.78, 1.26)], and group membership and Category Fluency [c = −7.06, SE = 0.89, 95% CI (−8.81, −5.31); c' = −2.56, SE = 1.72, 95% CI (−5.95, 0.82)]. In the case of Object Decision, the total effect was significant [c = −2.10, SE = 0.24, 95% CI (−2.57, −1.62)] and this direct effect was significantly lessened or partially mediated by HIHD [c' = −0.99, SE = 0.47, 95% CI (−1.91, −0.07), p = 0.03].

DISCUSSION

In advanced PD, we demonstrate a strong cultural bias on psychometric testing favoring individuals born in Anglosphere countries over first-generation immigrants born in other countries. This bias is observed on several measures of visuoperception and executive functioning, including JLO, Silhouettes, Object Decision, WCST, Matrix Reasoning, Category Fluency, and a trend is noted in complex visuoconstruction on the ROCF copy. However, no significant effect of culture is evident on measures of auditory attention (Digit Span), verbal and visual memory (CVLT-II and ROCF recognition), and spatial working memory (CALT). Of the potential contributing factors, disease-related and demographic characteristics do not account for the noted cultural bias as these are similar between groups, and immigration variables and English proficiency also do not relate significantly to performance in the International group. Notably, we demonstrate that the socio-development context specific to the time and place of birth of our participants strongly contributes to cultural bias on cognitive testing. Indeed, the Historical Index of Human Development (HIHD) mediates the relationship between group and performance completely for four biased tasks, and partially for one task.

Together, our findings have important implications for cross-cultural cognitive neuroscience as they demonstrate that culture has differential effects across cognitive domains (with visuoperception being particularly vulnerable), and that the HIHD captures important aspects of this cultural effect. Our results are also highly relevant for clinical neuropsychology practice in PD as well as in other neurological conditions. We discuss these points as well as study limitations in turn.

Cultural Bias and Cognitive Domains

It may be surprising that some of the most striking, consistent biases are seen on tests of basic visuoperception as well as executive tasks utilizing visual stimuli (WCST, Matrix Reasoning), in which verbal abilities play little or no role, rather than on tasks with a prominent language component (e.g., CVLT-II and Digit Span). This runs counter to common clinical practice in neuropsychology which emphasizes the use of non-verbal tests, presumed to be less biased than verbal tasks, in assessing culturally diverse populations

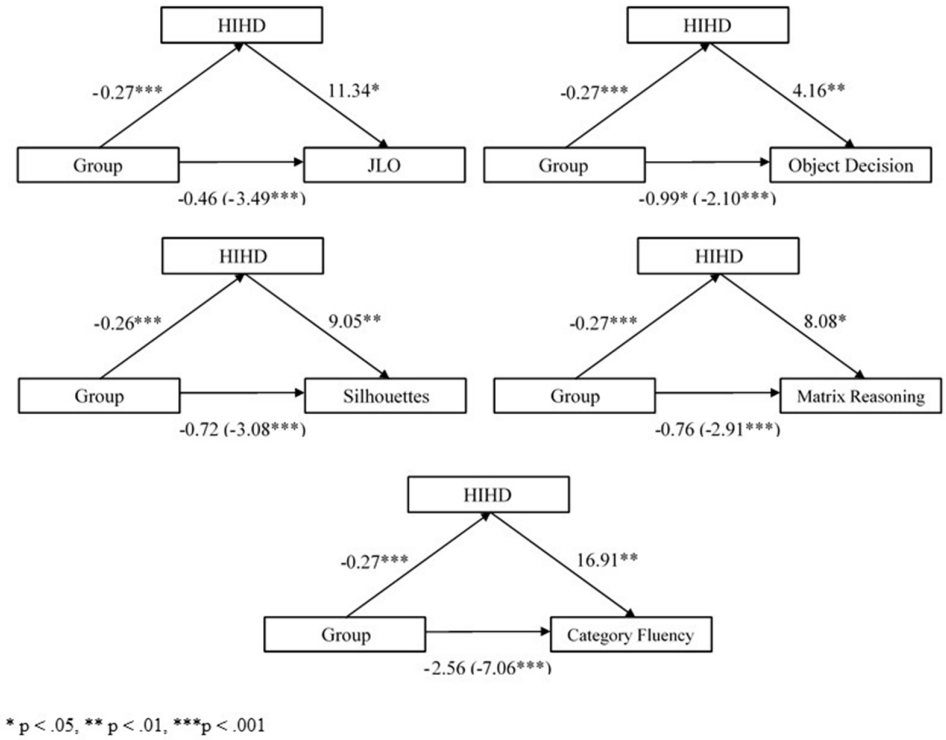

FIGURE 2 | Mediation models for group membership (x), Historical Index of Human Development (HIHD; M), and performance on biased tasks (y).

(for review, see Rosselli and Ardila, 2003). In fact, many "culture-fair" tests of general intellectual functioning [e.g., Cattell's Culture Fair Test (Cattell, 1940), Raven's Progressive Matrices (Raven and Court, 1998), Test of Nonverbal Intelligence (TONI; Brown et al., 1990), Naglieri Nonverbal Ability Test (NNAT; Naglieri, 2003)] contain non-verbal abstract reasoning tasks similar to the Matrix Reasoning subtest of the Wechsler scales, where we find a significant cultural bias. One factor to be considered when interpreting these results relates to differences in semantic knowledge of the visual stimuli between cultures, an issue which Luria noted following his expedition to Uzbekistan in 1931 (for description, see Nell, 1999). Certainly the two VOSP tasks do utilize common objects whose prototypical form may vary slightly between cultures (e.g., a kettle, a purse). But importantly, our participants have been exposed to Canadian culture and Anglosphere-typical representations of these objects for nearly three decades, and there is no relationship between the number of years in Canada and performance on these tasks. This finding is similar to results showing that years in Denmark did not influence performance on several visuoconstruction tasks (including Clock Drawing) among Turkish immigrants (Nielsen and Jørgensen, 2013). Moreover, it is also difficult to apply this explanation to the JLO where individuals are simply asked to match the angles of two lines, which does not seem to rely on semantic knowledge.

These findings are, however, consistent with a growing cognitive neuroscience literature recognizing that visuospatial abilities are not immune to cultural effects. For example, susceptibility to basic visual illusions, color perception, and visual attention vary between cultures (Masuda, 2009) but it remains unclear to what extent these difference reflect item, method, and/or construct bias of the tasks (Van de Vijver and Tanzer, 2004) vs. underlying neurobiological mechanisms. While our Anglosphere group outperformed the International group on all visuoperceptual tasks, there is evidence that individuals from other cultures do perform better on some experimental tasks tapping different aspects of visuospatial abilities (e.g., mental rotation in Chinese speakers, Li and O'Boyle, 2011; Li et al., 2014). However, we are unaware of any clinical visuospatial tasks where non-Anglosphere individuals have an advantage, and this is likely related to where and how clinical measures are conceived, created, and standardized. Therefore, it seems that experimental findings from the cognitive neurosciences have yet to translate to clinical practice, and this will be key to the development of "culture-fair" tests.

Cultural bias is also observed in Category Fluency, despite the fact that it was administered in the patients' language of choice and that the open-ended nature of the cues (i.e., Animals and Boys Names) allows the generation of exemplars reflecting participants' culture. This task has been recommended for use in cross-cultural neuropsychology (Ardila et al., 2006) as comparable performance is observed in older adults across different Spanish-speaking countries (Ostrosky-Solis et al., 2007) and between monolinguals and bilinguals in a multicultural

setting (Luo et al., 2010). However, there is also evidence of cultural bias in some immigrant groups, and like our groups, is not related to time since immigration (Nielsen et al., 2012; Nielsen and Waldemar, 2016; Peviani et al., 2016). Perhaps the speeded nature of the task, which is the only timed task analyzed, may be a contributing factor as the emphasis on speed can vary across cultures (Ardila, 2005).

As for other cognitive domains, no significant bias is noted in attention span, working memory, and episodic memory despite the verbal nature of some tasks (Digit Span, CVLT-II), or the visuoperceptual nature of others (ROCF recognition, CALT). The literature is inconsistent with respect to the cultural effect on attention span and working memory, with evidence showing both significant (Ostrosky-Solís and Lozano, 2006) and null effects (Hedden et al., 2002). As for episodic memory, it is generally accepted that core episodic memory abilities are universal given strong evidence that medial temporal lobe (MTL) lesions reliably lead to profound memory loss. Differences in perception and semantic knowledge as noted above can, however, influence the specific characteristics of the stored memory representations (Gutchess and Indeck, 2009), although this did not translate in performance differences on the tasks used here.

Human Development Index as a Measure of Culture

We found that countries' Human Development level captures aspects of culture that accounts for a significant proportion of the noted bias on cognitive test performance examined here. This is a novel way to address culture in the field of cross-cultural neuropsychology, and we are aware of only two other studies that have used this variable to explain cognitive test performance. Berg et al. (2017) found that in a sample of young people with psychosis, high values on the original UN-HDI predicted better executive functioning scores among individuals with Norwegian heritage and first-generation immigrants to Norway. These findings are relevant to our current study in a number of ways. First, there is an overlap between the measures used in both studies (e.g., Category Fluency, Matrix Reasoning, and Digit Span) and in findings (e.g., strong relationship between HDI and executive tasks). Second, this study was conducted in Norway, which has a high HDI but is not an Anglosphere country where neuropsychological tests are typically conceived. Moreover, immigrants in this study moved to Norway before school age, completed all of their education within the Norwegian educational system, and were fluent in a Scandinavian language. In contrast, participants in our International group typically immigrated to Canada as adults and thus, completed all or most of their education in their home country. Despite these differences in the potential level of acculturation, age, and disease, both studies demonstrate a relationship between HDI and cognitive test performance suggesting that early life within specific socio-developmental contexts has a strong and long-lasting impact on cognitive testing. The second study demonstrated that Latin Americans' performance on a widely used test of cognitive effort, the Test of Memory Malingering (TOMM), was strongly correlated with UN-HDI of the eight countries in which they resided (Nijdam-Jones et al., 2017). The authors warn about the cross-cultural applicability of the TOMM and especially the use of North American cut-off scores in other populations. Therefore, though it may seem like a crude measure that ignores intra-country diversity (albeit intra-country HDI metrics do exist for some countries) and is far from encompassing all aspects of a society and its culture, human development nonetheless relates to cognitive test performance and can help elucidate why and how cognitive abilities differ across cultures.

Relevance to Clinical Neuropsychology

The presence of cultural bias on neuropsychological testing has important implications for the field of neuropsychology at large as psychometric testing is used clinically to diagnose conditions such as MCI and dementia and to determine the degree of neurocognitive compromise across different disorders. For instance, in neurodegenerative disease research, this bias likely impacts epidemiological studies estimating prevalence, and the investigation of biomarkers and risk factors for poor cognitive prognosis. Studies in Alzheimer's disease (AD) and related MCI illustrate this. Despite controlling for numerous factors, the prevalence of MCI and dementia varies greatly across the world (Sachdev et al., 2015) and across race/ethnic groups within the USA (Katz et al., 2012; Ferraro, 2016). Part of the issue may be related to the use of biased tests and/or inappropriate norms. For example, when North American norms are applied to people from other countries (namely, Morocco, Spain, and Colombia), up to 51% of individuals are misdiagnosed with MCI or dementia, albeit diagnoses in this study were solely based on psychometric data without considering self- or family-reports of cognitive decline (Daugherty et al., 2017). In terms of prognostication, different patterns of cognitive performance may predict eventual conversion to dementia in different ethnic/racial groups (Weissberger et al., 2013). As for biomarkers, a pertinent example is that the correspondence between the degree of MTL atrophy in MCI and the magnitude of cognitive dysfunction on testing varies across race/ethnicity despite controlling for various risk factors (DeCarli et al., 2008; Burke et al., 2018; Weissberger et al., 2019). It is reasonable to assume that cultural bias on testing has a similar impact on MCI and dementia in PD. To our knowledge, there are no studies other than ours addressing this directly, however, a recent study aimed at identifying tests that consistently detect cognitive decline in PD is particularly relevant (Hoogland et al., 2018). Neuropsychological data of 2,908 non-demented PD patients from 20 international studies and nine countries (USA, Canada, New Zealand, Australia, Spain, Italy, Netherland, Germany, and Taiwan) were pooled, and although the cognitive domains affected were consistent with the PD literature (memory, executive dysfunction and attention), no specific tests were recommended due to high between-study variability. It is unclear whether the inclusion of societal context variables (e.g., HIHD) could help reduce this heterogeneity and if so, whether it could be used as a correcting factor in multicultural and international collaborative studies. For example, several authors have used regression models to "correct" test scores for individual differences (i.e., age, education, sex; Cavaco et al.,

2013a,b; Casaletto et al., 2016; Abou-Mrad et al., 2017; Alobaidy et al., 2017; Kirsebom et al., 2019). A similar correction approach may be adopted with the HIHD or other societal variables in future studies.

In addition to diagnosis, cultural bias also affects the evidence supporting the identification of risk factors. It is well recognized that research productivity, including that in psychology (Arnett, 2008; Henrich et al., 2010) and neurology (Jamjoom and Jamjoom, 2016), is geographically biased with a strong proportion of published studies coming from the USA and other Anglosphere countries. Within these studies, diversity of research participants is also reduced by a selection bias. This applies to the few studies investigating risk factors for cognitive decline in PD. For instance, a cognitive phenotype consisting of visuospatial deficits and poor category verbal fluency has been associated with rapid progression to PD dementia (Foltynie et al., 2004; Williams-Gray et al., 2007, 2013). This study was completed in Cambridgeshire England, and the patient group was identified to be 98% Caucasian. Given our results showing cultural bias on Category Fluency and visuospatial functioning, the two main characteristics of the "at-risk" phenotype, it is unclear whether performance on these tasks would retain its predictive value in more culturally diverse patient groups.

Importantly, while we demonstrate a significant bias on psychometric tests, it did not translate in increased rates of PD-MCI/dementia because these diagnoses require the presence of subjective cognitive complaints and the frequency of such reported cognitive decline did not differ between our groups. Based on our results, Daugherty et al.'s (2017) findings of elevated misdiagnoses of MCI and dementia in Morocco, Spain and Colombia may be overestimated because reports of cognitive decline were not required for diagnosis assignment. This highlights the importance of not solely relying on psychometric data for diagnostic purpose, but also integrating information on the reported course of cognitive change and their impact on daily function for individual patients. However, it is important to note that individuals' perception of their own cognition, mood, and general health, and their subjective complaints are not free for cultural bias either (Karasz, 2005; Jürges, 2007; Mograbi et al., 2012; Wu, 2016; Molina, 2017; Rossouw et al., 2018).

Limitations

In terms of limitations of the current study, several other factors previously identified as contributors to cultural bias on cognitive testing are not accounted for. First, other than education and occupational attainment (in Canada or abroad), other indicators of socio-economic status such as current wealth or income are not available. Although most individuals come to Canada under the economic class category, current poverty remains higher in this group relative to Canadian-born individuals [i.e., chronic low income is 4.8% in Canadian-born vs. 13.2% in Toronto immigrants even 15–20 years after landing (Lu and Picot, 2017)].

Second, because our study is retrospective, we do not have specific measures of English proficiency other than whether English is a first language or whether an interpreter provided assistance with the assessment. It is unclear which measure would be appropriate given linguistic differences across English-speaking countries and regions, and we question whether this would account for the noted group differences given that no bias was found on some tasks involving verbal material (e.g., CVLT-II). Similarly, we do not have information on whether participants in both groups are bi- or multi-lingual and to what degree of proficiency. This may be relevant in light of research, in part conducted in Toronto, on the beneficial effect of bilingualism to executive functioning (Bialystok et al., 2008; Nielsen et al., 2019) and its potential protective effect from age-related cognitive decline (Bialystok et al., 2014).

Third, we also did not measure the degree of acculturation other than by the number of years in Canada, which is frequently used as a proxy of acculturation with the caveat that it does not necessarily reflect cultural incorporation (Fox et al., 2017). Relatedly, we do not consider potential acculturation or cultural effects in the Anglosphere group, which likely includes a high proportion of second-generation immigrants given that this reflects 28% of Toronto's population (Statistics Canada, 2017). Transgenerational cultural effects have been documented in general health research (Fox et al., 2015) and neuropsychological studies (Kemmotsu et al., 2013; Bossuroy et al., 2014; Ferraro, 2016), thus our study may actually underestimate the cultural effect on cognitive tests. While acculturation is an important factor to consider in future studies, several challenges have been identified in integrating such measures in health research, as illustrated by conflicting findings attributed to inconsistent conceptualization and operationalization across studies (Fox et al., 2017). Measuring acculturation in highly diverse societies such as Toronto is further complicated because it requires consideration of hybrid or fusion culture(s) in addition to the original and host cultures, and as such, the bi-dimensional instruments commonly used are not appropriate (Fox et al., 2017).

Lastly, we also do not examine our data in the framework of East/West or individualistic/collectivist traits, often used in cross-cultural psychology. Of note, no consistent pattern of cognitive performance appeared between East (Asia) and West (Anglosphere or Europe) regions (**Supplementary Figure S1**).

CONCLUSION

In sum, lasting cultural biases exist on neuropsychological tests in first-generation immigrants with PD despite significant exposure to, and participation in, Canadian culture. While previously identified contributing factors such as education, English proficiency, and verbal nature of the tasks do not account for this bias, we provide compelling evidence that the socio-development and historical context in which individuals are born is a strong and persistent contributor. At a coarse level, being born in Anglosphere countries, which share cultural and historical roots, and similar high levels of economic and social development offers an advantage on cognitive tests that are typically conceived in these regions. A finer and scalable metric of human socio-development borrowed from the field of Development Economics, namely the HIHD, robustly mediates this relationship. Hence, the integration of such societal

indices has strong potential to benefit research in cross-cultural psychology. For the current practice of clinical neuropsychology, our findings underscore the need to suspect the presence of cultural bias when assessing immigrants, particularly those originating from countries with low human development index, irrespective of their English proficiency, educational and professional attainment, or length of time since immigration.

DATA AVAILABILITY

The datasets for this study will not be made publicly available because this consists of clinical data and we did not request permission from the REB to share data outside our institution.

ETHICS STATEMENT

This study conforms to the standards set by the latest revision of the Declaration of Helsinki and was approved by the Research Ethics Board of the University Health Network.

AUTHOR CONTRIBUTIONS

MS and MC designed the study, extracted data from clinical charts, interpreted data, and wrote the manuscript. MC performed statistical analyses.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00269/full#supplementary-material

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OPINION
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"Seeing Color," A Discussion of the Implications and Applications of Race in the Field of Neuroscience

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Between 1986 and 2006, the number of North American institutions offering undergraduate degrees in Neuroscience increased 20-fold. This boost mirrored the modern wave of Neuroscience, dubbed by the United States Congress as the "Decade of the Brain."

However, the true emergence of the discipline of brain science dates long before the 2000s, finding its roots in the theorems and postulates of some of the most celebrated minds in the fields of Psychology, Biology, and related disciplines. Neuroscience has established its presence as a strong force in the scientific community, far surpassing the shelf life characteristic of a common pseudoscience, but some say the field has yet to undergo the meticulous scrutiny that more long-standing disciplines have endured; an evaluative process which includes a review of the ethical implications and impact of the field itself.

With the ever-progressing code of ethics and morality in modern society, one integral component has been the discussion of the inclusion and representation of marginalized identities within the scientific community, and how—for better or for worse—scientific disciplines have evolved from their original culture of the perennial "old boys club," welcoming only the most racially and historically privileged individuals in society. The question that this brings up, that this commentary is designed to tackle, is whether these same discussions around diversity in the wider realm of science have happened and should happen in the field of Neuroscience.

By examining both the historical and present-day dynamics of this field, this manuscript examines whether the Neuroscience community has successfully been held accountable for its actions, or whether the attempt to remain "objective" has, in essence, resulted in harmful complicity in the perpetuation of scientific racism.

IN THE HISTORY BOOKS

Many of the modern-day discoveries within the fields of Psychology and Neuroscience still pay homage to the methodologies and theorems developed decades before. This reverence, however, brings into question the extent to which the glorification of the historical figures behind these theories conveniently overlooks some of their more problematic beliefs.

In the late nineteenth century, Dutch and German scientific duo Gustav Fritsch and Eduard Hitzig gained recognition for their behavioral research that led to a deeper understanding of the motor cortex and basal ganglia. Fritsch and Hitzig are canonically lauded as scientific pioneers for their contributions to the model of motor function. It is a lesser known fact, however, that Fritsch's anthropological explorations and research were motivated by his quest to find proof of the genetic superiority of the white race. Fritsch's ethnographic work allowed him to travel to countries around Europe and Southern Africa, where he spent months at a time collecting eye and hair evidence aimed at finding an anthropological basis for the genetic inferiorities of "negroes" (Gross, 2012).

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This erasure is not restricted to a single scenario: upon further research, it becomes clear that even a handful of names one might find in a History of Neuroscience syllabus had more than a few, often lesser-known controversial ideological stances. David Hume, Scottish philosopher and contributor to *Discourse on Brain and Consciousness,* stated "I am apt to suspect the negroes, and in general all the other species of men to be naturally inferior to the whites. There never was a civilized nation of any other complexion than white, nor even any individual eminent either in action or speculation" (West, 2003). Immanuel Kant, metaphysicist and inspiration behind Kantian Neuroscience, once said, "Among the hundreds of thousands of blacks who are transported elsewhere from their countries… still not a single one was ever found who presented anything great in art or science or any other praiseworthy quality, even though among the whites some continually rise aloft from the lowest rabble, and through superior gifts earn respect in the world" (West, 2003). And Voltaire, French Enlightenment philosopher and influencer of *Theory of Mind,* wrote "The Negro race is a species of men as different from ours as the breed of spaniels is from that of greyhounds," in his essay "The People of America" (West, 2003).

Students are often taught about the integral contributions of these scientists, including their experiments, methods, and even some of their *academically* contentious stances. But little to no light is cast on their ideological viewpoints, some of which served as key motivators and components of their overall bodies of academic work.

But where do we draw the line between brilliance and ignorance?

It is undeniable that, in many ways, these scientists have been the backbone of Modern Neuroscience, individuals whose knowledge and prestige precede them. However, we cannot solely acknowledge the positive and/or beneficial aspects of their legacy, but should also recognize the importance of identifying the successes *and* shortcomings which, together, make up their bodies of belief. This legacy of accurate and holistic representation becomes all the more important when considering how race and ethnic diversity is represented within Neuroscience research itself.

NEUROSCIENCE OF RACE

In recent years, many of the Natural Sciences have delved into the practice of investigating "social" issues from an empirical perspective. This discipline, dubbed "cultural neuroscience," has examined behavioral phenomena related to prejudice, social segregation and the like, to help us understand how our attitudes form (Choudhury and Kirmayer, 2011; Martínez et al., 2012). As highlighted in some of the systematic reviews done on current literature in the field, these studies have outlined the behavioral schema by which we associate and subsequently react to variations in race, gender, and other phenotypic characteristics (Ronquillo et al., 2007; Richeson et al., 2008; Martínez et al., 2012). Such research has confirmed that factors such as Cross-Race Effect and Implicit Bias can explain the unconscious assumptions we make about different groups, and neurological responses that occur when confronted with people different from ourselves (Phelps et al., 2003; Wheeler and Fiske, 2005; Kubota et al., 2012). Applying these findings to our understanding of everyday social encounters, this research has provided objective evidence challenging the preconceived notion of racism as a fictitious experience.

However, this empirical approach could lead to the pathologization of racism, presenting it as a clinical matter of evolutionary advantage rather than as problematic behavior (Rose and Rose, 2001; Martínez et al., 2012). By depicting of a man's hatred for his immigrant neighbor as a specified pattern of activation in fusiform face area and amygdala rather than an act of ignorance and hatred, we create a much more docile interpretation of the situation, which negates and justifies the potential violence of one human's emotions toward another.

Additionally, the attribution of cultural difference to physical distinction is the very belief from which early scientific practices such as Phrenology, Physiognomy and Trepanation found their footing. Phrenology, a field created by Franz Joseph Gall in the late eighteenth century, was centered around the idea that the brain could be divided into an aggregated map, topographically organized into characteristics and traits. With this ideology came many levels of prejudicial assumptions on the mental capacities and differences of various ethnic and racial groups, with whiteness often being centered as the "pinnacle specimen of intelligence" (Gross, 2012; Staum, 2014). Similar racial iterations propagated the popularity of scientific documents such as *Crania Americana*, which many justified the implementation of the Trans-Atlantic Slave Trade and labor exploitation of black and brown bodies.

Although this same line of reasoning may not be explicitly employed today, a key element for the "weaponization" of the scientific findings of that age was the lack of accountability on the part of the scientist for the implications of their research. The conclusions drawn at a lab bench or computer desk—a controlled environment in which the members of that cohort adhere to a certain united ethical code—does not always similarly translate when published to the larger population. These scientific ideas and conclusions can be warped and manipulated, and in some cases, even used to push dangerous agendas of racial and cultural hierarchy. This is one benefit of having diverse perspectives within the research community, which facilitates consideration of the overarching influence of research, and examination of whether marginalized voices have been given a space within field's framework.

NEUROSCIENCE AND RACE

While it is important to talk about the applications of race within the data, it is also critical that we evaluate the application of racial literacy within the Neuroscience community. Just as the brain is composed of bundles of individual neurons and synapses, a scientific field is equal to the sum of its parts: principal investigators, research assistants and technicians, post-doctoral scholars, and undergraduates.

Statistically speaking, Underrepresented Minorities (URMs) comprise only 7.7% of the larger scientific community in the United States of America (Higher Education Training., 2013), with an even smaller percentage of this subpopulation (<2%) counting black and Hispanic women (Matchett, 2013; Guterl, 2014). But even these numbers are a far cry from the minuscule demographic representation of the past. In a 1974 governmental study, it was found that 94% of neuroscientists were white, with a mere 1.8% representing the cumulative total of all URM's in the field (2011, Higher Education Training., 2013). As it stands today, Neuroscience appears (on paper) to still be a very white, male, western-dominated field: within academia, URMs represent only 12% of pre-doctoral students, 4% of postdocs, and 6% of all tenure-track faculty across Neuroscience departments nationwide (Higher Education Training., 2013). While these numbers are shocking, they are not surprising considering the historical landscape of access and availability. A little over 3 decades ago the Society for Neuroscience (SfN), the largest Neuroscience society in the world, had <4% of their entire member body identify as racial minorities, a fact that incited the development of diversity initiatives such as the Neuroscience Scholars Program (NSP) in an effort to bolster recruitment (Matchett, 2013; Research Funding, 2018). Even with these initiatives and platforms, however, the numbers show that significant work is still to be done before the playing field is level for all.

The more prominent instances of minority representation in research are not often from the investigator's side, but rather in the populations utilized to conduct the research. Both early and modern Neuroscience, like many other research fields, have made use of the most "available" subject populations to collect data, which usually entailed exploiting lower socioeconomic status (SES) communities and People of Color (POC's), who were often less protected and more at risk. In the past, this has included the use of groups categorized as "vulnerable populations," including prisoners, mentally unstable patients, and other marginalized groups (pregnant women, fetuses, institutionalized patients, etc.) (Fiscella et al., 2000; Backlar, 2002). Many of these vulnerable population groups intersect with the smaller black and brown communities most easily accessible to researchers, individuals who had little to no say or knowledge of the true cost of their involvement as research participants. Examples of this range far and wide: the Holmesburg Prison experiments, Tuskegee Experiments, and MKUltra. Any and all methods of recruitment and experimentation, regardless of the long-term effects, were excusable as long as the scientific potential was promising.

Although copious ethical standards and guidelines have been put in place to ensure the ethical disgraces of the past are not repeated, "subject baiting" still takes place, if not more inventively: nowadays one may see the "make a quick buck" study ads pop up on street poles, in their local bulletin, or on their social media feeds, with little to no information on the specific parameters of the study that potential participants are being encouraged to volunteer for. Often, the first motive of the participating populations is the financial incentive with the only prerequisite being a willingness to have their body used and/or exploited.

Discrepancies in inclusivity can be examined in the everyday practices of research labs, as exemplified by the "representative sample" conundrum: Oftentimes, participant samples recruited for studies fall into the category of being W.E.I.R.D (White, Educated, Industrialized, Rich, and Democratic) (Henrich et al., 2010). While these populations are easy to recruit, especially on college campuses, they are not representative of the general population. One must ask if the notion of "ease of subject access" is a sufficient enough claim to not expand our research conventions in a way that would champion both inclusive and ethical science, a notion that is applicable in the case of both the populations we research and the research cohorts themselves. In comparison to other scientific fields, Neuroscience, especially on an academic level, is small. This means that the disparities in racial diversity are even more pronounced, as reflected in the aforementioned mere 6% minority tenure-track Neuroscience professors across academic institutions. The most challenging part lies in the fact that the only way in which this dynamic can shift is if opportunities for minorities to enter the Neuroscience field are made apparent, and if these diverse individuals see a place for themselves within this field. Statistics from 2011 revealed that only 12% of applications to Neuroscience graduate programs came from ethnic minorities, in comparison to the 18% applying to medical school and 23% to graduate school programs in general (2017, Reports, 2018), emphasizing that Neuroscience is still decades behind other fields in incorporating diversity into their research community.

CONCLUSION

All in all, an examination of the dynamic between race and racial diversity within neuroscience will require a review of the historical treatment of minorities in the field. In order to fundamentally shift the field in the direction of equality, we have to focus efforts into making Neuroscience *equitable*—pursuing initiatives for the substantial amplification of diverse voices in the field until it becomes routine. Additionally, research practice can only progress when we consider that the work done thus far is still not sufficiently representative or universally appreciated. As long as we work in niches—"cultural neuroscience" instead of "neuroscience that reflexively integrates culture"—we remain limited as a field. If, however, the neuroscience community acknowledges its historical biases while reflecting upon current research practices and infrastructure, the field could become as dynamic, diverse, and ever-adapting as the very organ that it is dedicated to studying.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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MINI REVIEW
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The Effects of APOE and ABCA7 on Cognitive Function and Alzheimer's Disease Risk in African Americans: A Focused Mini Review

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African Americans have double the prevalence of Alzheimer's disease (AD), as compared to European Americans. However, the underlying causes of this health disparity are due to a multitude of environmental, lifestyle, and genetic factors that are not yet fully understood. Here, we review the effects of the two largest genetic risk factors for AD in African Americans: Apolipoprotein E (APOE) and ABCA7. We will describe the direct effects of genetic variation on neural correlates of cognitive function and report the indirect modulating effects of genetic variation on modifiable AD risk factors, such as aerobic fitness. As a means of integrating previous findings, we present a novel schematic diagram to illustrate the many factors that contribute to AD risk and impaired cognitive function in older African Americans. Finally, we discuss areas that require further inquiry, and stress the importance of racially diverse and representative study populations.

Keywords: African American (AA), APOE ε4, ABCA7, aerobic fitness, cognitive function, cognitive decline, Alzheimer's disease

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INTRODUCTION

African Americans are at an elevated risk of cognitive decline and memory loss, with double the prevalence of Alzheimer's disease (AD) as compared to European Americans (Logue et al., 2011; Barnes and Bennett, 2014; Alzheimer's Association, 2019). The underlying causes of this health disparity are not sufficiently understood. Apolipoprotein E (APOE) and ABCA7, two genes involved in lipid metabolism, are the strongest heritable contributors to AD in African Americans (Reitz et al., 2013). However, the influence of genetic risk on environmental and behavioral risk factors, and their combined effects on AD biomarkers in African Americans, is yet to be determined. Furthermore, little is known about the neural substrates of cognition in older African Americans and how they relate to genetic risk factors for AD.

Here, we review recent work outlining two distinct ways genetic risk impacts AD biomarkers in African Americans. First, we examine the direct effects of genetic variation on neural correlates of cognitive function, such as activation and functional connectivity from functional magnetic resonance imaging (fMRI) studies. Second, we discuss the indirect effects of genetics on brain structure and function, *via* interaction with modifiable risk factors for AD, specifically aerobic fitness.

African Americans are at an increased risk of cardiovascular disease (Obisesan et al., 2012), which has been established as an important predictor for AD (Izquierdo-Porrera and Waldstein, 2002). Management or improvement of cardiovascular risk factors through increased aerobic

fitness and exercise can reduce the risk for cognitive decline and dementia (Baumgart et al., 2015). Consistent with this, low levels of physical activity is one of the most prevalent risk factors for AD (Norton et al., 2014; Cass, 2017). In particular, African Americans have lower rates of physical activity as compared to European Americans (Gothe and Kendall, 2016; Benjamin et al., 2019). As such, aerobic fitness and exercise may be more viable modifiable factors to attenuate the risk for AD in African Americans.

It is important to delineate the difference between AD as determined by neuroimaging, biofluid biomarkers, or autopsy, as compared to the clinical diagnosis of Alzheimer's and related dementias. However, to remain aligned with the terminology of the original cited works, throughout this review we refer to both instances as AD.

DIRECT EFFECTS OF GENETICS

APOE

The APOE ε4 allele is one of the strongest genetic risk factors for AD (Potter and Wisniewski, 2012). APOE functions to regulate lipid metabolism in the brain by mediating the uptake of lipoproteins; in particular, it modulates the clearance of amyloid-β (Aβ; Di Paolo and Kim, 2011). Both dysfunctional cholesterol processing and Aβ aggregation have been implicated in AD pathogenesis (Schultz et al., 2017). In European Americans, the APOE ε4 allele has been associated with 2–3 times the risk of AD in heterozygotes and 12 times the risk in homozygotes (Michaelson, 2014). African Americans have a higher frequency of the APOE ε4 allele (Logue et al., 2011; Barnes and Bennett, 2014), and ε4 homozygosity is highly associated with AD in African-ancestry groups (Hendrie et al., 2014). However, the results are inconsistent for heterozygotic carriers (Farrer et al., 1997), with some studies suggesting that APOE ε4 may have less predictive impact on AD outcomes in African-ancestry populations, including African Americans (Rajabli et al., 2018). Despite the mixed nature of these findings, APOE ε4 has been associated with increased risk of late onset AD (LOAD) in African Americans (OR = 2.31; 95% increased risk; Reitz et al., 2013).

APOE ε4 has also been linked to episodic memory-related dysfunction in the medial temporal lobe (MTL; Bookheimer et al., 2000; Filippini et al., 2009; Dennis et al., 2010; Michaelson, 2014), one of the earliest brain regions impacted by the progression of AD. APOE ε4 genotype and amyloid-induced synaptic pathology have been related to accelerated rates of AD pathology within the MTL (Potter and Wisniewski, 2012), particularly in hippocampal sub-regions in both rodent and human models (Palmer and Good, 2011).

Pattern separation—the ability to independently represent and store similar experiences by reducing mnemonic interference (Leal and Yassa, 2018)—relies on MTL function. As such, one way to characterize decline into mild cognitive impairment (MCI) and AD is by a shift away from pattern separation towards pattern completion, which is mediated by dysfunctional hippocampal hyperactivity (Yassa et al., 2011b). Impaired mnemonic discrimination is associated with atypical hyperactivation in the dentate gyrus (DG) and CA3 hippocampal subfields (Dickerson et al., 2005; Yassa et al., 2011a,b; Reagh et al., 2017) in healthy older adults (Toner et al., 2009; Stark et al., 2013) and those with MCI (Yassa et al., 2010; Bakker et al., 2012, 2015; Tran et al., 2017).

Research examining the impact of APOE ε4 genotype on MTL function, *via* performance on a mnemonic discrimination task, has yielded mixed results in different racial populations with varying degrees of cognitive impairment. A study in MCI patients reported no differences in hippocampal hyperactivation or mnemonic discrimination based on APOE ε4 status (Tran et al., 2017). Conversely, AD patients that were homozygotic carriers of the APOE ε4 allele performed worse on challenging mnemonic discriminations (Wesnes et al., 2014). When examining spatial mnemonic discrimination across cognitively impaired and unimpaired older adults, impaired ε4 carriers performed worse than unimpaired carries and either group of non-carriers (Sheppard et al., 2016).

These previous studies were primarily conducted in European American cohorts and/or did not report the specific racial breakdown of their subject pools. In a population of cognitively healthy older African Americans, there were APOE ε4-related impairments in mnemonic discrimination, coincident with hyperactivity in the left DG/CA3 and the CA1. Although the overall effect of APOE ε4 on AD outcomes in African Americans remains unclear (Farrer et al., 1997; Tang et al., 2001; Hendrie et al., 2014; Rajabli et al., 2018), this result may suggest that APOE ε4-related hippocampal dysfunction can manifest in healthy older African Americans and may be an indicator of future disease status.

While APOE ε4 is associated with a moderately increased risk for progression from MCI to AD-type dementia (Elias-Sonnenschein et al., 2011), it may not alter the disease progression during the preclinical period (Bondi et al., 1999; Bunce et al., 2004). However, the effect of APOE ε4 in the preclinical phase may be contingent on other factors such as the level of amyloid aggregation (Mormino et al., 2014) and homozygotic vs. heterozygotic status (Caselli et al., 1999). Clinically normal carriers of APOE ε4 with high levels of amyloid aggregation experienced the highest levels of cognitive decline as compared to ε4 non-carriers and those with lower Aβ aggregation (Mormino et al., 2014). Cognitively healthy APOE ε4 homozygotic carriers also experienced memory decline earlier than heterozygotic carriers (Caselli et al., 1999).

ABCA7

Outside of APOE, ABCA7 is the strongest genetic risk factor for AD in African Americans (Reitz et al., 2013). As a member of the super-family of adenosine triphosphate (ATP)-binding cassette (ABC) transporters, ABCA7 is another gene that regulates the homeostasis of phospholipids and cholesterol in the central nervous system and peripheral tissues. ABCA7 gene expression has been linked to AD *via* the dysregulation of lipid metabolism (Zhao et al., 2015; Aikawa et al., 2018).

ABCA7 single nucleotide polymorphism (SNP) rs115550680 is associated with the development of LOAD in African Americans with an effect size (OR = 1.79; 70%–80%

increase in risk) that is comparable to that of APOE ε4 (Reitz et al., 2013). ABCA7 rs115550680 is hypothesized to contribute to AD in African Americans through amyloid precursor protein (APP) processing and the suppression of Aβ clearance (Cukier et al., 2016).

In cognitively healthy elderly subjects and MCI patients, cortical Aβ load is associated with disrupted functional connectivity within the MTL and impaired memory performance (Song et al., 2015). As such, Aβ plaques may play a key role in facilitating tauopathy in the MTL, and therefore lead to disrupted functional connectivity in the MTL circuitry. Hardy and Selkoe (2002) suggest that one of the functions of ABCA7 in AD may be Aβ facilitated tauopathy: as Aβ deposition accumulates in cortical regions within the default mode network (DMN), it may lead to concurrent accumulation of tau tangles in the MTL *via* reciprocal connections through the entorhinal cortex (EC) (Pooler et al., 2015). Hence, the cortico-MTL circuit may be the neural network underlying ABCA7 rs115550680-related AD pathology.

A recently published study examining the impact of ABCA7 rs115550680 genotype on the cortico-MTL network function in a group of cognitively healthy older African Americans found ABCA7-related dissociation in EC resting state functional connectivity (Sinha et al., 2019). Specifically, the risk variant was associated with increased functional connectivity between the EC and other MTL regions, including hippocampal subfields, coincident with decreased connectivity between the EC and medial prefrontal cortex (mPFC; Sinha et al., 2019). These findings suggest that for individuals with the risk ABCA7 rs115550680 genotype, impaired cortical connectivity leads to a more functionally isolated EC at rest, which translates into aberrant EC-MTL hyper-synchronization (Sinha et al., 2019).

While direct claims cannot be made about the exact mechanism underlying the aforementioned alterations in cortico-MTL network function, when considering the relevance of Aβ in ABCA7-related AD pathogenesis, these results may reflect the combined reinforcement between amyloid and tau pathology in the EC (Sinha et al., 2019). Thus, anomalous MTL functional connectivity may be an additional neural correlate of future cognitive decline in African Americans. This ABCA7 variant is monomorphic in European Americans (Reitz et al., 2013; Machiela and Chanock, 2015), and consequently, it does not confer any increased risk for AD in this group. However, recent studies of functional connectivity in MCI and AD patients have reported a similar disconnection of the MTL from other nodes of the DMN, particularly mPFC, but increased connectivity locally within the MTL, between EC and other subregions of the MTL (Das et al., 2013; Pasquini et al., 2015). As such, MTL network dysfunction may be a ubiquitously applicable AD biomarker for preclinical AD detection.

INDIRECT EFFECTS OF GENETICS

The Interaction With Aerobic Fitness

Modifiable lifestyle factors, such as diet, exercise, and aerobic fitness, contribute to AD risk. In particular, aerobic fitness is one cardiovascular disease management method that has been associated with decreased levels of cognitive decline and reduced risk of AD in several previous studies (Colcombe and Kramer, 2003; Kramer et al., 2005, 2006). Aerobic activity has been found to aid in brain lipid homeostasis and in the reduction of Aβ deposit accumulation (Maesako et al., 2012; He et al., 2017; Houdebine et al., 2017). Recent work has also argued that increased levels of aerobic fitness can attenuate the adverse influence of AD-related polygenic vulnerability derived from genes implicated in lipid homeostasis, including APOE and ABCA7 (Schultz et al., 2017).

In addition to ABCA7 rs115550680 (reviewed under Direct Effects of Genetics), which has been identified as a genetic risk factor for AD in African Americans, another ABCA7 SNP (rs3764650) has been identified as a susceptibility locus for AD in European Americans (Hollingworth et al., 2011; Naj et al., 2011). ABCA7 rs3764650 has a lower effect size in African Americans (OR = 1.23), increasing AD risk by about 10%–20% (Reitz et al., 2013). However, this SNP has been found to influence overall ABCA7 expression (the conversion of DNA instructions into functional products and proteins), and, dysfunctional ABCA7 expression levels are associated with AD risk (Vasquez et al., 2013; Aikawa et al., 2018).

While the overall effects of ABCA7 rs3764650 on cognition seem to be minimal (Vivot et al., 2015; Andrews et al., 2016, 2017), it has been found to alter cognition in subgroups stratified on factors such as gender and disease progression. In healthy elderly, an association between rs3764650 and cognitive decline was found selectively in females (Nettiksimmons et al., 2016), and, in individuals with a final diagnosis of MCI or AD, this SNP was associated with increased rates of memory decline (Karch et al., 2012; Carrasquillo et al., 2015).

A study of healthy older African Americans found that ABCA7 rs3764650 modulates the association between aerobic fitness level (as measured by maximal oxygen consumption, VO_2 max) and mnemonic flexibility—the ability to flexibly apply and recombine information from past learning—as measured by generalization following rule learning (Berg et al., 2019). In particular, for carriers of the non-risk genotype, higher levels of aerobic fitness were significantly associated with fewer generalization errors. Conversely, carriers of the risk genotype did not show any relationship between aerobic fitness and generalization. Successful mnemonic flexibility is known to depend on the integrity of the MTL (Myers et al., 2002, 2008), a major site of neuroplasticity that is sensitive to the effects of exercise and aerobic fitness (Cotman et al., 2007). The results of Berg et al. (2019) therefore imply that the ABCA7 risk genotype may attenuate the neuro-protective value of aerobic fitness in cognitively healthy older African Americans.

Analogous to this study, others have found that in European Americans, APOE ε4+ individuals did not receive the same benefits as APOE ε4− individuals from higher levels of aerobic fitness or following an exercise intervention, with fitness only reducing the risk for dementia in non-carriers (Podewils et al., 2005; Lautenschlager et al., 2008). On the contrary, some self-reported studies of physical activity found that the neuro-protective effects of fitness were exclusive to APOE ε4 carriers (Schuit et al., 2001; Rovio et al., 2005; Smith et al., 2011).

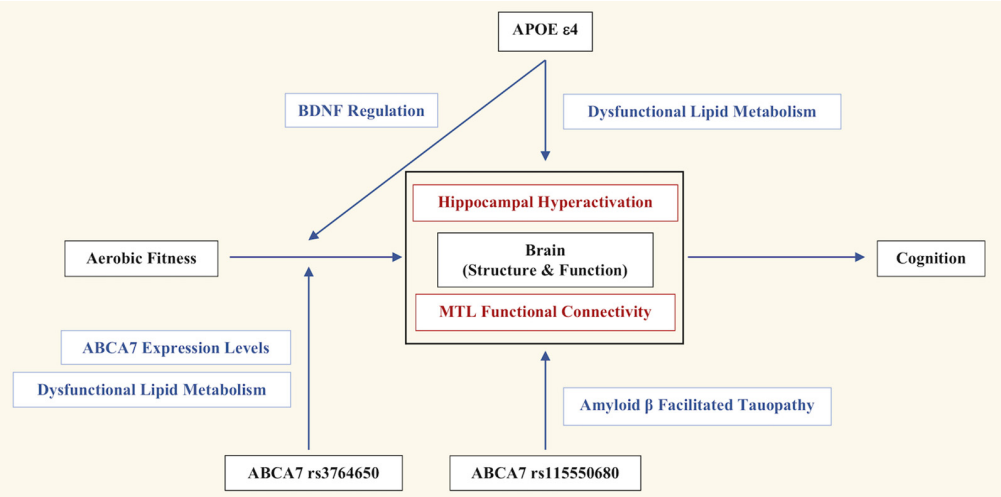

FIGURE 1 | The genetic and lifestyle factors that contribute to Alzheimer's disease (AD) risk and impaired cognitive function in African Americans. Overall, aerobic fitness influences brain structure and function, which then affects cognition. Apolipoprotein E (APOE) ε4 directly impacts brain structure and function *via* dysfunctional lipid metabolism, leading to aberrant hippocampal hyperactivation and therefore, impaired mnemonic discrimination of episodic memories. APOE ε4 indirectly influences the effects of aerobic exercise on hippocampal plasticity and volume through the regulation of BDNF. ABCA7 rs115550680 directly impacts the brain through amyloid-β (Aβ) facilitated tauopathy, which negatively influences medial temporal lobe (MTL) functional connectivity, and consequently, behavioral generalization. ABCA7 rs3764650 moderates the effects of aerobic fitness through dysfunctional lipid metabolism and ABCA7 expression, which indirectly impairs behavioral generalization.

Additionally, in African Americans the APOE ε4 genotype has been found to influence exercise-related upregulation of BDNF (brain-derived neurotrophic factor), a gene associated with neuroplasticity and hippocampal volume (Erickson et al., 2011); non-carriers of the ε4 allele exclusively experienced a significant increase in BDNF levels after 6 months of exercise, while carriers did not (Allard et al., 2017).

Research on the interactive effects of aerobic fitness and genetic risk for AD is still in the early stages, with the various studies containing methodological and racial differences in subject populations. Albeit equivocal, these results do provide evidence of the modulating effect of genetic variation on modifiable AD risk factors.

DISCUSSION

Here, we reviewed research outlining the influence of genetic risk on MTL neural and cognitive function. We present a novel comprehensive outline of how genotypic variation may contribute to AD and impaired cognitive function (**Figure 1**). Overall, aerobic fitness influences neural structure and function, which then affects cognition. APOE ε4 directly impacts the brain *via* dysfunctional lipid metabolism, leading to aberrant hippocampal hyperactivation, and therefore, impaired mnemonic discrimination of episodic memories (Sinha et al., 2018). The indirect effects of APOE ε4 *via* fitness remain somewhat ambiguous, with some studies reporting aerobic fitness-related benefits only in APOE ε4− individuals (Podewils et al., 2005; Lautenschlager et al., 2008; Allard et al., 2017), while other studies report those benefits only in APOE ε4+ individuals (Schuit et al., 2001; Rovio et al., 2005; Smith et al., 2011). However, exercise-induced upregulation of BDNF, and its influence on hippocampal plasticity, may serve as a possible mechanism for the indirect influence of APOE ε4 (Allard et al., 2017).

Meanwhile, ABCA7 rs115550680 directly impacts the brain through Aβ facilitated tauopathy, which negatively influences MTL functional connectivity, and consequently, behavioral generalization (Sinha et al., 2019). Although ABCA7 rs3764650 is not a causative variant for AD in African Americans, and does not directly impact brain structure and function, it appears to confer indirect consequences on cognition and AD risk by moderating the effects of aerobic fitness through dysfunctional lipid metabolism and ABCA7 expression (Berg et al., 2019).

While the current schematic (**Figure 1**) of genetic influences on AD risk in African Americans is a first step, additional studies are needed to verify the molecular mechanisms underlying the link between genetic risk and pathogenic pathways; the potential contribution of brain lipid homeostasis in the MTL should be a focal point. It is also important to determine if ABCA7 and APOE have any common pathways mediating the effect on MTL structure and function. Furthermore, comprehensive single-cell type transcriptome analyses in human and mouse brains may be necessary to determine cell-specific contributions of ABCA7 risk variants to AD pathogenesis. For instance, ABCA7 rs115550680-related dysregulation of lipid metabolism may specifically target the neurons accelerating APP processing and Aβ production, while, ABCA7 rs3764650 may impact Aβ clearance by the microglia, known to play a pivotal role in mediating exercise-dependent enhancement of hippocampal neurogenesis (Vukovic et al., 2012).

Several studies have shown qualitative and quantitative differences in AD between African Americans and European Americans. One such study found racial differences in cerebrospinal fluid (CSF) and structural MRI biomarkers of AD in an elderly cohort; despite comparable CSF Aβ42 levels, white matter hyperintensity (WMH) volume, and hippocampal volume, the same degree of WMH had a greater influence on cognition in African Americans as compared to European Americans (Howell et al., 2017). Since WMH is a marker of vascular dysfunction, which African Americans experience at a higher rate than European Americans (Obisesan et al., 2012), these results may indicate that genes such as APOE and ABCA7, which regulate lipid metabolism, differentially affect African Americans. For example, the direct and indirect effects of ABCA7 have not been validated in other racial groups. ABCA7 rs115550680 is monomorphic on the non-risk minor "A" allele in European Americans (Reitz et al., 2013; Machiela and Chanock, 2015). As such, ABCA7 rs115550680 may confer AD risk selectively in African Americans, and, in conjunction with the indirect effects of ABCA7 rs3764650, may contribute to the higher incidence rate of dementia and AD in this population.

It is imperative that the studies presented here be replicated across diverse subject populations for a more representative and comprehensive understanding of AD progression and outcomes. At the same time, it will be crucial for future studies to examine race-specific AD biomarkers and consequences. Finally, researchers should explore the interplay between genetic variation and other modifiable lifestyle factors, such as diet and sleep patterns, to understand whether the benefits of potential interventions are similar for those with and without a genetic risk for dementia and AD.

AUTHOR CONTRIBUTIONS

CB and NS conducted background research. CB drafted the manuscript. NS and MG provided critical review of the manuscript.

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Interactive Effects of Racial Identity and Repetitive Head Impacts on Cognitive Function, Structural MRI-Derived Volumetric Measures, and Cerebrospinal Fluid Tau and Aβ

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Background: Factors of increased prevalence among individuals with Black racial identity (e.g., cardiovascular disease, CVD) may influence the association between exposure to repetitive head impacts (RHI) from American football and later-life neurological outcomes. Here, we tested the interaction between racial identity and RHI on neurobehavioral outcomes, brain volumetric measures, and cerebrospinal fluid (CSF) total tau (t-tau), phosphorylated tau (p-tau$_{181}$), and Aβ_{1-42} in symptomatic former National Football League (NFL) players.

Methods: 68 symptomatic male former NFL players (ages 40–69; n = 27 Black, n = 41 White) underwent neuropsychological testing, structural MRI, and lumbar puncture. FreeSurfer derived estimated intracranial volume (eICV), gray matter volume (GMV),

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white matter volume (WMV), subcortical GMV, hippocampal volume, and white matter (WM) hypointensities. Multivariate generalized linear models examined the main effects of racial identity and its interaction with a cumulative head impact index (CHII) on all outcomes. Age, years of education, Wide Range Achievement Test, Fourth Edition (WRAT-4) scores, CVD risk factors, and *APOE*ε4 were included as covariates; eICV was included for MRI models. *P*-values were false discovery rate adjusted.

Results: Compared to White former NFL players, Black participants were 4 years younger (p = 0.04), had lower WRAT-4 scores (mean difference = 8.03, p = 0.002), and a higher BMI (mean difference = 3.09, p = 0.01) and systolic blood pressure (mean difference = 8.15, p = 0.03). With regards to group differences on the basis of racial identity, compared to White former NFL players, Black participants had lower GMV (mean adjusted difference = 45649.00, p = 0.001), lower right hippocampal volume (mean adjusted difference = 271.96, p = 0.02), and higher p-tau$_{181}$/t-tau ratio (mean adjusted difference = −0.25, p = 0.01). There was not a statistically significant association between the CHII with GMV, right hippocampal volume, or p-tau$_{181}$/t-tau ratio. However, there was a statistically significant Race x CHII interaction for GMV (b = 2206.29, p = 0.001), right hippocampal volume (b = 12.07, p = 0.04), and p-tau$_{181}$/t-tau ratio concentrations (b = −0.01, p = 0.004).

Conclusion: Continued research on racial neurological disparities could provide insight into risk factors for long-term neurological disorders associated with American football play.

Keywords: American football, biomarkers, chronic traumatic encephalopathy, cognitive function, concussion, magnetic resonance imaging, race, subconcussion

INTRODUCTION

Exposure to repetitive head impacts (RHI) from contact sports has been associated with later-life neurological disorders, including chronic traumatic encephalopathy (CTE) and other neurodegenerative diseases (McKee et al., 2013, 2016; Bieniek et al., 2015; Ling et al., 2017; Mez et al., 2017b; Adams et al., 2018; Tagge et al., 2018; Alosco et al., 2019a; Stern et al., 2019). Autopsy studies of convenience samples suggest that professional American football players may be at high-risk for later-life neurological disorders (McKee et al., 2013; Mez et al., 2017b). *In vivo* studies show that former National Football League (NFL) players have worse cognition, as well as greater structural, functional, and molecular brain alterations (Didehbani et al., 2013; Hart et al., 2013; Strain et al., 2015; Koerte et al., 2016a; Alosco et al., 2018c, 2019b; Lepage et al., 2018). These effects might extend to high school and college football players (Mez et al., 2017b), and other contact sport athletes (Koerte et al., 2012, 2015, 2016b; Ling et al., 2017). Yet, not all individuals exposed to RHI develop neurological disorders (Casson et al., 2014; Solomon et al., 2016; Deshpande et al., 2017; Baker et al., 2018; Willer et al., 2018; Zivadinov et al., 2018). Among those that do, there is heterogeneity in disease presentation, suggesting other risk factors are at play (McKee et al., 2013; Stern et al., 2013; Alosco et al., 2017c, 2018b; Mez et al., 2017b). These may include: age (McKee et al., 2013; Alosco et al., 2018c), age of first exposure (AFE) to RHI (Stamm et al., 2015a,b; Alosco et al., 2017b, 2018b; Schultz et al., 2017), cognitive reserve (Alosco et al., 2017c), and genetics (Stern et al., 2013; Cherry et al., 2018).

The effect of exposure to RHI on neurological disorders may also be modified by factors associated with race. Note that because the term *African-American* historically refers primarily to individuals descended from enslaved Africans in North America, we will use the term *Black* as it is inclusive of all individuals who are descended from sub-Saharan Africa regardless of specific ancestry or position within the broader African diaspora. Individuals who identify as Black are at increased risk for cognitive impairment, cognitive decline, and dementia, including Alzheimer's disease (AD) dementia (Potter et al., 2009; Barnes and Bennett, 2014; Gross et al., 2015; Hohman et al., 2016; Zahodne et al., 2016). *In vivo* MRI studies in older adults show that Black identifying individuals exhibit increased volume of white matter hyperintensities (Brickman et al., 2008) and differences in brain volumes compared to Whites (Sencakova et al., 2001; Brickman et al., 2008; Waldstein et al., 2017; Morris et al., 2019). Autopsy studies also link Black racial identity with increased risk for neuropathologic changes of AD and related diseases, including cerebrovascular disease (Graff-Radford et al., 2016; Filshtein et al., 2019). Although, some studies have failed to find an association between Black racial identity and AD pathologic changes (Riudavets et al., 2006; Wilkins et al., 2006; Morris et al., 2018) and risk for dementia

(Fillenbaum et al., 1998). A recent study also reported *decreased* CSF t-tau and p-tau$_{181}$ in Blacks compared to Whites (Morris et al., 2019). These racial neurological disparities have been attributed to the association of Black racial identity with lifestyle behaviors across the life course known to influence cognitive aging (e.g., poor diet, sedentary behaviors) (Morris et al., 2018), cardiovascular disease (CVD) (Newman et al., 2005; Jackson et al., 2013; Benjamin et al., 2019), genetics (e.g., *APOE*ε4 or *ABCA7* status) (Reitz et al., 2013; Graff-Radford et al., 2016; Rajan et al., 2019), socioeconomic status (Zahodne et al., 2017), and other factors (Barnes and Bennett, 2014; Zahodne et al., 2017; Brewster et al., 2018). Many of these factors associated with racial identity may influence both clinical and neuropathological outcomes, whereas others (e.g., socioeconomic status) might have more specific impact on clinical function (e.g., neuropsychological test scores, dementia risk).

Previous studies report that Black participants have worse functional outcomes after acute traumatic brain injury (TBI) (Gary et al., 2009). Associations between Black racial identity and neurological outcomes have been examined in the setting of *active*, but not former, contact sport play. For example, among 403 active University of Florida student-athletes, individuals who identified as being Black demonstrated worse memory and speed performance on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) (Houck et al., 2018). In the subset of football players, Black racial identity only predicted worse processing speed. Research among active collision sport athletes also provides evidence for racial identity as an independent correlate of serum concentrations of S100B, UCH-L1, and Aβ and cognitive test scores (Asken et al., 2018b).

Racial differences have also been reported in aging former NFL player samples, including higher overall and CVD-related mortality rates in non-White former NFL players (Lincoln et al., 2018). In two recent studies of former NFL players from the NIH-funded Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests (DETECT) study, our team found racial differences (via its inclusion as a model covariate) on white matter alterations on MRI (Alosco et al., 2018a), as well as on cerebrospinal fluid (CSF) levels of t-tau, p-tau$_{181}$/t-tau, and sTREM2 (a marker of microglial activation) (Alosco et al., 2018c). These findings could have key implications given Blacks have been overrepresented (relative to the general population) in American football, particularly at elite levels, for the past 4–5 decades (Lehman et al., 2012; Lehman et al., 2016; Lapchick and Marfatia, 2017; Lincoln et al., 2018; NCAA, 2018). The contribution of racial identity to later-life neurological outcomes associated with exposure to RHI is unknown. Here, we tested the effects of the interaction between racial identity and a novel metric of exposure to RHI (the cumulative head impact index [CHII]) (Montenigro et al., 2017) on neurobehavioral outcomes, white and gray matter volume, and CSF concentrations of t-tau, p-tau$_{181}$ and Aβ_{1-42} among symptomatic former NFL players from the DETECT study. Our overall hypothesis was that Black racial identity and the CHII would interact to have synergistic, negative impacts on neurobehavioral and neurological functioning.

MATERIALS AND METHODS

Participants and Study Design

The sample included symptomatic former NFL players from the NIH-funded DETECT study. The primary objective of the DETECT study was to provide an initial examination of risk factors and *in vivo* biomarkers for CTE. Investigation of racial disparities was not a primary objective of the DETECT study and the current study represents secondary data analyses on differences between racial identity groups using data collected from DETECT. Recruitment and enrollment began in 2011 and concluded in 2015. Former NFL players were recruited using several different methods, including emails to and presentations for members of the NFL Players Association and/or NFL Alumni Association, social media postings through the Boston University (BU) Alzheimer's Disease and CTE Centers, and word of mouth. Inclusion criteria for the former NFL players included: male, ages 40–69, a minimum of two seasons in the NFL and a minimum of 12 years of organized football, and self-reported complaints of cognitive, behavior, and/or mood symptoms at the time of telephone screening. For self-reported complaints, participants were eligible if they affirmatively responded to having any (i.e., absence or presence) cognitive, behavioral, or mood symptoms. Former NFL players were required to have subjective complaints in order to maximize the likelihood of having underlying CTE neuropathology to thereby facilitate risk factor and biomarker detection. Exclusion criteria included MRI and/or lumbar puncture (LP) contraindications, presence of another central nervous system (CNS) disease, and/or a primary language other than English. Twenty-eight same-age asymptomatic individuals without a history of contact sport participation or TBI were recruited to serve as a "control" group for the DETECT study (Stern et al., 2016; Alosco et al., 2017a, 2018a,c). However, this "control" group was not included in this study because only 1 participant self-identified as Black, thereby limiting the ability to conduct reliable study group comparisons as a function of racial identity.

All participants completed a single 2–3 days study visit, which involved administration of neuropsychological tests, neurological and psychiatric evaluations, LP, blood draw for *APOE* genotyping and other biomarker analysis, MRI, and history interview. Additional descriptions of the DETECT study have been reported previously (Alosco et al., 2017a,d, 2018a,c; Stern et al., 2016). All study protocols were approved by the Boston University Medical Center Institutional Review Board. The Partners Healthcare Human Research Committee approved all neuroimaging procedures. Participants provided written informed consent prior to participation.

Measures

Neuropsychological and Neuropsychiatric Function

A neuropsychological test battery, and semi-structured interviews and self-report measures of neuropsychiatric function

were administered to participants on a separate day from the LP. A full list of the tests administered as part of DETECT has been presented elsewhere (Alosco et al., 2017a). As part of this battery, participants were administered the Wide Range Achievement Test, Fourth Edition (WRAT-4). Standard scores of this measure were included in this study to operationalize early-life educational quality. The neuropsychological battery also included measures of attention, psychomotor speed, executive function, verbal and visual memory, language and visuospatial abilities, as well as gross motor functioning. Neuropsychiatric status was also evaluated, including symptoms of depression, suicidality, hopelessness, apathy, aggression, impulsivity, and hostility. To limit the number of analyses, principal component analysis (PCA) was performed to generate the following four neurobehavioral factor scores: psychomotor speed and executive function, verbal episodic memory, visual episodic memory, and behavioral/mood. The four factor scores were examined as outcomes. The derivation of the factor scores has been published elsewhere (Alosco et al., 2017a). Note that raw neuropsychological test scores were converted to standardized scores using normative data that accounted for age; for three of the tests, the normative data also accounted for education, along with age (i.e., Trail Making Test Parts A and B, and Controlled Oral Word Association Test). Race was not accounted for in the standardization procedures. The standardized scores were used in the PCA to form the factor scores.

Magnetic Resonance Imaging

All participants underwent structural MRI on a 3-Tesla MRI Scanner (Verio, Siemens Healthcare) with a 32-channel head array and the Syngo MR-B17 software suite. T1-weighted images were acquired with a magnetization-prepared rapid gradient echo sequence: TR = 1800 ms, TE = 3.36 ms, voxel size = 1 × 1 × 1 mm, acquisition matrix = 256 × 256, flip angle = 7°. The quality of the T1-weighted images was evaluated through visual inspection. Automated segmentation of volumes from the T1-weighted images was done using FreeSurfer 5.3[1]. This segmentation resulted in an automated Talairach transformation, segmentation of deep gray matter structures (including hippocampus), and parcellation of the cerebral cortex, based on gyral and sulcal structures (Desikan et al., 2006; Fischl et al., 2004a,b). Following the automated volumetric segmentation, quality assessment was performed to ensure the fit and completeness of the obtained FreeSurfer parcellation. Using this automated method in FreeSurfer, we obtained estimated total intracranial volume (eICV), total gray matter volume (GMV), total cortical white matter volume (WMV), total subcortical gray matter volume (sGMV), right and left hippocampal volume, and volume of white matter hypointensities. Manual correction of the hippocampus using Slicer 4.1[2] (Fedorov et al., 2012) was performed using procedures described elsewhere (Lepage et al., 2018). eICV served as a covariate, whereas the other volumetric measures were examined as outcomes. The hippocampus and WM hypointensities were selected *a priori* due to previous work showing their associations with race (Brickman et al., 2008; Sencakova et al., 2001; Waldstein et al., 2017; Morris et al., 2019) and neurodegenerative disease (Bobinski et al., 2000; Sencakova et al., 2001; Tosto et al., 2015).

[1]http://surfer.nmr.mgh.harvard.edu

[2]http://www.slicer.org/

CSF Analytes

CSF (15–20 ml) was obtained by LP in the morning after overnight fasting. LPs were performed by the study neurologist using an atraumatic 25-guage Sprotte needle at either L3/L4 or L4/L5. After aspiration, approximately 10 ml of CSF was deposited into a polypropylene transfer tube and frozen at -80°C. Aliquots were shipped to the University of Pennsylvania for batch analysis of t-tau, p-tau$_{181}$, and Aβ_{1-42}. Methods of CSF biomarker analysis of t-tau, p-tau$_{181}$, and Aβ_{1-42} are described elsewhere (Shaw et al., 2009; Grossman et al., 2014; Deters et al., 2017; Alosco et al., 2018c). Concentrations of these analytes served as outcomes for markers of neurodegeneration (t-tau), hyperphosphorylated tau (p-tau$_{181}$), and amyloidosis (Aβ_{1-42}). We also examined the p-tau/t-tau and p-tau/Aβ_{1-42} ratios. The p-tau/t-tau ratio has been shown to be sensitive to the detection of certain neurodegenerative diseases, such as frontotemporal lobar degeneration (FTLD) (Meeter et al., 2018). The p-tau/Aβ_{1-42} ratio has also been identified as a sensitive predictor of AD (Fagan et al., 2007; Racine et al., 2016). Inclusion of these ratios will thereby increase our ability to draw inferences on suspected underlying etiologies.

Cumulative Head Impact Index (CHII)

The CHII was used to quantify and define exposure to RHI, with higher CHII scores reflecting greater exposure to RHI (Montenigro et al., 2017). This index is based on the reported number of football seasons played, position[s] played, and levels played (e.g., youth, high school, college), as well as estimated head impact frequencies derived from published helmet accelerometer studies. For a description of the development of the CHII, refer to Montenigro et al. (2017). Because published helmet accelerometer data does not exist at the professional level, college-level estimates of head impact frequencies were extrapolated and applied to the current sample of former NFL players to estimate their post-college head impact frequencies.

Cardiovascular Disease Assessments

Blood pressure was taken for all participants and height and weight were measured to calculate BMI using the standard formula: weight (kg)/height^2 (m). Diagnostic history of CVD risk factors were self-reported (absence or presence).

Racial Identity

Participants self-reported racial identity. They were asked, "What race do you consider yourself (primarily)?" Participants selected from the following options, consistent with racial categories from the 2010 US Census: White, Black or African American, American Indian, Alaska Native, Asian, Native Hawaiian/Pacific Islander, or Other. As with the 2010 Census, participants were able to select multiple racial identities, although this was not explicitly stated as an option. No other racial categories were selected by participants within the sample, and no individuals self-identified as both White and Black.

TABLE 1 | Sample characteristics.

	Total sample (*N* = 68)	Black former NFL players (*n* = 27)	White former NFL players (*n* = 41)	P[a]
Demographic and athletic history				
Age, mean (SD) years	54.69 (8.16)	52.15 (7.63)	56.37 (8.15)	0.04
Education, mean (SD) years	16.50 (1.00)	16.44 (0.93)	16.54 (1.05)	0.71
Learning disability, n (%)	3 (4.6)	1 (4.0)	2 (4.9)	1.00
WRAT-4 standard scores, mean (SD)	98.91 (10.51)	94.07 (10.52)	102.10 (9.31)	0.002
Years of football play, mean (SD) years	18.54 (3.26)	18.37 (2.86)	18.65 (3.53)	0.74
Years in the NFL, mean (SD)	8.16 (2.61)	8.30 (2.69)	8.07 (2.58)	0.73
Cumulative Head Impact Index, mean (SD)	20394.65 (6500.78)	18798.24 (5843.83)	21445.95 (6762.75)	0.10
Age of first exposure to football, mean (SD)	11.71 (2.54)	12.15 (2.52)	11.41 (2.54)	0.25
Primary Position Group, n (%)				
Offensive line	20 (29.4)	6 (22.2)	14 (34.1)	0.25
Running back	7 (10.3)	8 (18.5)	2 (4.9)	
Tight end	4 (5.9)	1 (3.7)	3 (7.3)	
Offensive skill	1 (1.5)	0	1 (2.4)	
Defensive line	11 (16.2)	4 (14.8)	7 (17.1)	
Linebacker	13 (19.1)	4 (14.8)	9 (22.0)	
Defensive Back	12 (17.6)	7 (25.9)	5 (12.2)	
Cardiovascular and *APOE* status				
Body mass index, mean (SD) kg/m^2	32.45 (4.86)	34.31 (5.47)	31.22 (4.02)	0.01
Systolic blood pressure, mean (SD)	130.53 (15.70)	135.67 (18.38)	127.15 (12.81)	0.03
History of hypertension, n (%)	31 (45.6)	13 (48.1)	18 (43.9)	0.69
History of diabetes, n (%)	5 (7.4)	4 (14.8)	1 (2.4)	0.08
APOE allele status, n (%) ε4 + (at least one copy)	22 (32.4)	11 (40.7)	11 (26.8)	0.23

[a]*Independent samples t-tests compared Black and White participants on all continuous outcomes. Chi-square was used to compare Black and White participants on primary position (linemen vs. other), history of hypertension, history of hypercholesterolemia, and APOE status (ε4 carriers vs. non-carriers). Fisher's Exact Test (due to small cell sizes) was used to compare Black and White participants on history of learning disability, and history of diabetes. Final sample sizes after exclusion for missing data: Learning disability: N = 65.*

TABLE 2 | Neuropsychological and structural MRI descriptives.

	Black former NFL players			White former NFL players		
	Mean (*SD*)	95% CI	Median	Mean (*SD*)	95% CI	Median
Principal component factor z-scores[a]						
Psychomotor speed/executive function	−0.47 (0.78)	−0.78, − 0.16	−0.56	0.29 (0.72)	0.06,0.52	0.40
Verbal episodic memory	−0.24 (0.58)	−0.47, − 0.01	−0.38	0.03 (0.99)	−0.28,0.34	−0.14
Visual episodic memory	0.13 (0.91)	−0.23,0.49	0.24	0.06 (0.94)	−0.23,0.36	0.18
Behavior/mood	0.25 (0.87)	−0.10,0.59	0.19	0.32 (0.90)	0.04,0.60	0.26
Volumetric measures,[b] mm^3						
Total gray matter volume	589163.82 (30457.77)	577115.12,601212.51	588030.59	640877.24 (46013.98)	626353.44,655401.05	634792.25
Total cortical white matter volume	464470.34 (41742.96)	447957.38,480983.31	452985.42	496324.79 (45649.58)	481916.01,510733.58	495873.36
Total subcortical gray matter volume	55937.15 (4584.69)	54123.51,57750.79	55260.00	55448.95 (4001.86)	54185.95,56712.09	55059.00
Right hippocampal volume	3312.04 (292.15)	3196.47,3427.61	3309.00	3407.27 (420.40)	3274.57,3539.96	3443.00
Left hippocampal volume	3333.89 (335.40)	3201.21,3466.57	3379.00	3379.46 (392.35)	3255.62,3503.30	3347.00
Volume of white matter hypointensities	2299.99 (2558.85)	1287.74,3312.24	1470.90	2016.88 (1420.44)	1568.54,2465.23	1622.50

[a]*Neuropsychological tests evaluated attention, executive function, verbal and visual episodic memory, language, and visuospatial function. Semi-structured interviews and self-report measures of neuropsychiatric function (e.g., depression, apathy, aggression) were completed. Raw scores were transformed to standard scores using normative data calibrated for age; for three tests (Trail Making Test Parts A and B, Controlled Oral Word Association Test) normative data accounted for education, along with age. Principal component analysis resulted in composite scores for psychomotor speed/executive function, verbal memory, visual memory, and behavior/mood domains. Lower scores represent worse performance for all factor scores, except for behavior/mood where higher scores reflect greater behavior and mood symptoms.*
[b]*Volumetric measures were derived from FreeSurfer. Manual correction of the hippocampus using Slicer 4.1 (http://www.slicer.org/) was performed.*

Sample Size

The original sample included 96 symptomatic former NFL players from the NIH-funded DETECT study. The sample size for the present study was reduced to 68 (27 identified as Black and 41 as White) following restriction of the sample to those who had complete data on the primary independent and dependent outcomes of interest. Missingness was most common for the dependent variables. For the neurobehavioral factor scores, the sample size was reduced due to missing data on the individual tests that comprise the factor scores. There was missingness for MRI outcomes due to the exclusion of participants who did not undergo MRI (e.g., because of claustrophobia) and for those whose T1-weighted MRI acquisition was of inadequate quality due to motion artifact. There was missingness across the CSF analytes due to exclusion of participants who, following enrollment, refused to undergo an LP, as well as immunoassay quality control failure. There were no differences between the analytic sample (N = 68) and those excluded in terms of age, years of education, racial identity, or CHII score (p's > 0.05 for all).

Statistical Analyses

Independent sample t-tests and chi-square analyses were used to compare Blacks and Whites on demographic, athletic, medical, and *APOE* variables. Our previous research reported on the main effects of exposure to RHI on neurological outcomes in the DETECT sample (Alosco et al., 2018a,c). In this more focused sample of DETECT participants, we focused on the interaction between racial identity and the CHII. We conducted three separate multivariate generalized linear models (GLMs) with an unstructured outcome correlation matrix to determine the Race x CHII interaction effect on the following: (1) the four neurobehavioral factor scores (psychomotor speed and executive function, verbal episodic memory, visual episodic memory, and behavioral/mood); (2) MRI-derived volumetric measures (GMV, sGMV, WMV, right and left hippocampal volume, and WM hypointensities); and (3) CSF analytes (t-tau, p-tau$_{181}$, p-tau$_{181}$/t-tau, Aβ_{1-42}, p-tau/Aβ_{1-42}). The primary independent variables included the binary racial identity variable and the continuous CHII variable. GLMs were used because they do not make assumptions of the correlation structures of the outcomes and account for correlations between outcomes from the same participant. The models estimate all pairwise correlations between each predictor and each outcome. The outcomes were grouped in a multivariate model based on the construct being assessed. For example, for the neurobehavioral factor scores model, all four factor scores were included as dependent variables and we obtained an estimate for each predictor (e.g., each covariate, racial identity, Race x CHII) on each of the individual factor scores. Given the large number of hypotheses tested, we controlled the False Discovery Rate (FDR) using the BH procedure for all main and interactive associations of racial identity and Race x CHII (Benjamini and Hochberg, 1995).

All models controlled for age, years of education, WRAT-4 scores, *APOE* status (ε4 carriers vs. non-carriers), and CVD risk factors (i.e., BMI, systolic blood pressure, diagnostic history of diabetes). These covariates were *a priori* selected based on the literature showing their association with race and the neurological outcomes being studied. Estimated ICV was included as covariate for all models with MRI-derived volumetric measures as outcomes to account for individual differences in head size. As mentioned previously, the goal of the DETECT study was not to assess racial disparities and therefore detailed assessment of cultural, psychosocial, and socioeconomic variables was not performed.

RESULTS

Sample Characteristics

Table 1 shows demographic, athletic, medical, and *APOE* characteristics for the Black and White former NFL players. Compared to White former NFL players, Black former NFL players were ∼4 years younger, had lower WRAT-4 scores, had a higher BMI, and had a higher systolic blood pressure. Note that the distribution of racial identity by within sample CHII severity scores (i.e., low, medium, high) included: Low had 9 White participants and 8 Black participants, medium had 17 White participants, and 15 Black participants, and the high exposure group had 15 White participants but only 4 Black participants. This is somewhat consistent with our **Table 1** finding of lower, but not statistically significant different, CHII scores in Black participants compared to White participants. A descriptive summary of neurobehavioral functioning, MRI-derived volumetric measures, and CSF analyte concentrations for Black and White former NFL players is presented in **Tables 2**, **3**.

TABLE 3 | Cerebrospinal fluid biomarker concentrations.

	Black former NFL players			White former NFL players		
	Mean (*SD*)	**95% CI**	**Median**	**Mean (*SD*)**	**95% CI**	**Median**
t-tau (pg/ml)	27.59 (7.26)	24.72,30.46	27.00	37.24 (15.12)	32.47,42.02	33.00
p-tau$_{181}$ (pg/ml)	19.78 (7.59)	16.77,22.78	21.00	18.46 (11.06)	14.97,21.96	16.00
Aβ_{1-42} (pg/ml)	334.52 (72.16)	305.97,363.06	333.00	376.49 (77.32)	352.08,400.89	384.00
p-tau$_{181}$/t-tau (pg/ml)	0.72 (0.25)	0.62,0.82	0.74	0.51 (0.23)	0.43,0.58	0.45
p-tau$_{181}$/Aβ_{1-42} (pg/ml)	0.06 (0.02)	0.05,0.07	0.06	0.05 (0.03)	0.04,0.06	0.04

t-tau, total tau; p-tau$_{181}$, hyperphosphorylated tau; Aβ, beta-amyloid.

Covariate Effects

For the neurobehavioral factor scores, older age was associated with lower visual memory (β = −0.36, p = 0.01) and behavioral/mood (β = −0.38, p = 0.01) factor scores. Higher WRAT-4 scores contributed to the prediction of higher psychomotor speed and executive function (β = 0.37, $p < 0.01$) and verbal memory (β = 0.31, p = 0.03) factor scores. *APOE* ε4 carriers had lower visual memory scores (mean difference = 0.64, p = 0.01) compared to non-carriers. Higher BMI corresponded to lower psychomotor speed and executive function factor scores (β = −0.32, p = 0.01).

For the MRI-derived volumetric measures, older age was associated with lower left (β = −0.28, p = 0.03) and right (β = −0.29, p = 0.002) hippocampal volume, as well as greater volume of WM hypointensities (β = 0.30, p = 0.02). Higher systolic blood pressure was also associated with lower right hippocampal volume (β = −0.26, p = 0.02). Estimated ICV correlated with GMV (β = 0.49, $p < 0.01$) and WMV (β = 0.38, $p < 0.01$).

For the CSF analytes, the only association was between older age and higher CSF t-tau concentrations (β = 0.29, p = 0.03).

There were no statistically significant effects for years of education on the outcomes.

Race × CHII Effects

In terms of significant differences as a function of racial identity, compared to White former NFL players, Black participants had lower GMV (mean adjusted difference = 45649.00, p = 0.001), lower right hippocampal volume (mean adjusted difference = 271.96, p = 0.02), and higher p-tau$_{181}$/t-tau ratio (mean adjusted difference = −0.25, p = 0.01). See **Table 4**, as well as **Figure 1** for box plots of group differences. There was not a statistically significant association between the CHII and these outcomes (i.e., GMV, right hippocampal volume, p-tau$_{181}$/t-tau ratio) in the entire sample. As shown in **Table 5**, there was a statistically significant Race x CHII interaction for the same outcomes for which there were race group main effects: GMV (p = 0.001), right hippocampal volume (p = 0.04), and p-tau$_{181}$/t-tau ratio (p = 0.004). **Figure 2** plots the race group differences on these outcomes based on CHII severity scores (i.e., low, medium, and high). There were no other statistically significant interaction effects. As shown in **Figure 2**, race group differences became magnified among those with higher CHII scores for GMV and CSF p-tau$_{181}$/t-tau ratio; although, there was not such a linear effect for right hippocampal volume.

TABLE 4 | Summary of multivariate generalized linear models comparing black and white symptomatic former NFL players on neurobehavioral measures, MRI-derived volumetric measures, and CSF levels of beta-amyloid, total tau, and P-tau.

	Beta (unstandardized)	Standard error	*T*-value	*P*-value (FDR-adjusted)
Neurobehavioral function				
Psychomotor speed/Executive function	0.45	0.21	2.14	0.15
Verbal memory	0.28	0.26	1.07	0.58
Visual memory	0.001	0.27	0.00	0.99
Behavior/Mood	0.13	0.25	0.51	0.82
Volumetric measures				
Total gray matter volume	45649.00	11000.00	4.15	0.001
Total cortical white matter volume	29686.00	12969.00	2.29	0.05
Total subcortical gray matter volume	190.45	1237.81	0.15	0.88
Right hippocampal volume	271.96	96.42	2.82	0.02
Left hippocampal volume	146.65	107.11	1.37	0.21
Volume of white matter hypointensities	−1204.35	582.43	−2.07	0.06
CSF analytes				
t-tau	4.73	3.67	1.29	0.20
p-tau$_{181}$	−4.83	2.97	−1.63	0.18
Aβ_{1-42}	33.32	23.36	1.43	0.20
p-tau$_{181}$/t-tau	−0.25	0.07	−3.40	0.01
p-tau$_{181}$/Aβ_{1-42}	−0.02	0.01	−2.00	0.05

Three separate multivariate Generalized Linear Models were performed to examine the racial identity differences on neurobehavioral variables, MRI-derived volumetric measures, and CSF analytes. All analyses controlled for age, years of education, WRAT-4 scores, body mass index (BMI), systolic blood pressure, history of diabetes, APOE status (ε4 carriers vs. non-carriers), and the cumulative head impact index (CHII). The MRI volumetric models also controlled for estimated intracranial volume. For neurobehavioral measures, lower scores are worse for all measures except for behavior/mood where higher scores are worse. Race is coded as 1 = Black and 0 = White and the beta estimates shown are White – Black. Abbreviations: FDR, false discovery rate; t-tau, total tau; p-tau, phosphorylated tau; Aβ, beta-amyloid.

DISCUSSION

In this sample of symptomatic former NFL players, higher levels of exposure to RHI (as defined by the CHII) and Black racial identity had an interactive effect on GMV, right hippocampal volume, and CSF p-tau$_{181}$/t-tau ratio concentrations. Although there was not a statistically significant association between CHII scores with these outcomes, Black former NFL players had lower GMV, lower right hippocampal volume, and higher CSF p-tau$_{181}$/t-tau ratio concentrations compared to White former NFL players. There were no statistically significant main or interaction effects on the neurobehavioral factor scores. All effects were independent of age, years of education, WRAT-4 scores, CVD risk factors, *APOE*ε4, and eICV (for MRI models). Further research is needed to clarify the nuanced role of racial neurological disparities in this setting by examining the role of socioeconomic, psychosocial, environmental, and genetic variables that were not measured in this study.

Black former NFL players who had high CHII scores also had higher (on average) p-tau$_{181}$/t-tau concentrations. P-tau$_{181}$

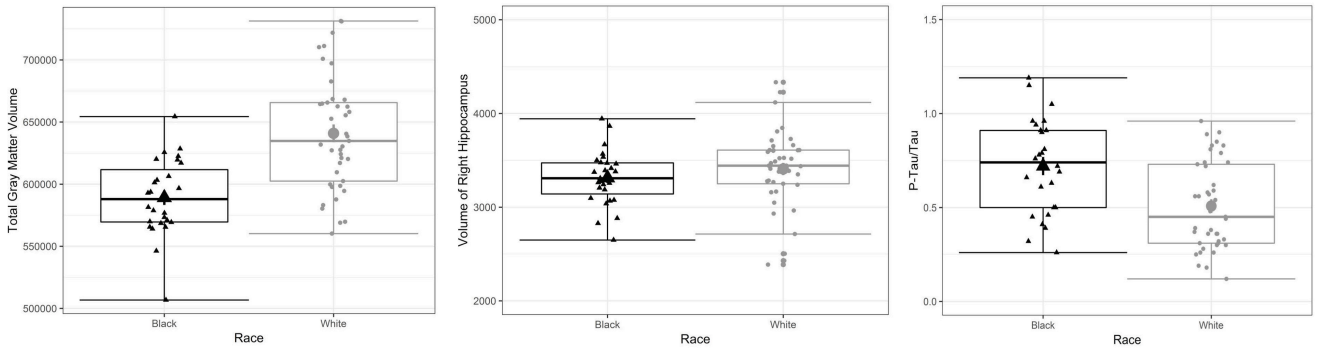

FIGURE 1 | Box Plots on Differences Between Black and White Former NFL Players on Total Gray Matter Volume, Right Hippocampal Volume, and CSF p-tau$_{181}$/t-tau. The mid-point line in the box represents the median, the interquartile range box represents the middle 50%, and the whiskers represent the bottom and top 25% of data values. The box plots show unadjusted associations. The multivariate generalized linear models showed a statistically significant main effect for race on these outcomes (FDR-adjusted *p*-value less than 0.05) after controlling for age, years of education, WRAT-4 scores, body mass index (BMI), systolic blood pressure, history of diabetes, and *APOE* status (ε4 carriers vs. non-carriers). Estimated intracranial volume (ICV) was also included as a covariate for total gray matter volume and right hippocampal volume.

is a biomarker of NFTs and the p-tau$_{181}$/t-tau ratio has been shown to be a sensitive biomarker for the detection of tauopathies that are similar to CTE (e.g., FTLD) (Meeter et al., 2018). It is interesting that there was a specific Race x CHII effect for CSF p-tau$_{181}$/t-tau but not t-tau or p-tau$_{181}$. This could be indicative of an early neurodegenerative disease process among the subset of Black participants who have higher levels of exposure to RHI. Individuals who identify as Black have been shown to have decreased resistance to neurodegenerative disease pathology (Graff-Radford et al., 2016; Filshtein et al., 2019). Exposure to RHI from contact sports has also been associated with CTE and other neurodegenerative diseases (McKee et al., 2013; Bieniek et al., 2015; McKee et al., 2016; Alosco et al., 2019a; Ling et al., 2017; Mez et al., 2017b; Adams et al., 2018; Tagge et al., 2018; Stern et al., 2019). Not everyone who is exposed to RHI will develop later-life neurological disorders. Previous fluid biomarker research by our team (Alosco et al., 2018c) and others (Asken et al., 2018b) emphasizes that other risk factors are likely at play, which may include those that occur more frequently in individuals with Black racial identity (e.g., CVD, low SES). In this study, the CHII only had an association with CSF p-tau$_{181}$/t-tau ratio through its interaction with Black racial identity. Explanations for the lack of effects of the CHII on p-tau$_{181}$ (and other CSF biomarkers) in the DETECT sample have been provided elsewhere (Alosco et al., 2018c). There was not a Race x CHII effect on Aβ_{1-42} or p-tau$_{181}$/Aβ_{1-42}, nor were there race group differences for Aβ_{1-42}. While such findings argue against an AD pathway, racial identity and RHI likely have independent and combined associations with mixed neurodegenerative disease processes that cannot be disentangled here. Inferences specifically regarding CTE cannot be made given it cannot yet be diagnosed during life and the utility and validity of *in vivo* fluid and imaging biomarkers in CTE remain unclear (Stern et al., 2019).

Although Black participants had lower GMV and right hippocampal volume compared to White participants, there was not a main effect of CHII on these outcomes and the magnitude and direction of the interaction between race and CHII was less clear compared to CSF p-tau$_{181}$/t-tau, particularly for right hippocampal volume (see **Figure 1**). There were also no other Race x CHII interaction effects. Our pattern of findings could be a consequence of being statistically underpowered, particularly given that there were few Black participants who had high CHII scores. Alternatively, recruitment and eligibility methods for the DETECT study were not designed to examine issues pertaining to race. Our recruitment (e.g., postings and presentations to the NFL Players and Alumni Associations, social media postings through our academic center outlets) and eligibility (e.g., English-speaking only) methods may have resulted in enrollment of socioeconomically and culturally homogeneous participants. Participants were also recruited based on self-reported symptomatic status, which was done via informal assessment and not quantitated. It is unclear if there were racial group differences in recruitment based on symptoms. Helmet accelerometer data from the college level were also extrapolated and used for this professional sample, which may have underestimated the effects of RHI, particularly at the professional levels. Other RHI exposure variables are also not included in the CHII (e.g., severity, interval rest, impact location). There are possible conceptual explanations, including that any effects observed were subclinical; this is supported by the largely normal neuropsychological test performance in the sample. Previous research among collegiate athletes has also shown that the association between CNS pathology (based on serum biomarker concentrations) and clinical function may actually be mediated by racial identity (Asken et al., 2018a). Lastly, because all of the former NFL players had extreme levels of exposure to RHI, this common risk factor might attenuate any pre-existing racial group differences and Race by CHII interactions that might exist for some neurological markers.

We *a priori* selected covariates associated with race and neurological outcomes. Age made a significant contribution to the prediction of many of the outcomes. *APOE* status, WRAT-4

TABLE 5 | Summary of multivariate generalized linear models examining the interaction between race and CHII on neurobehavioral measures, MRI-derived volumetric measures, and CSF levels of beta-amyloid, total tau, and P-tau.

	Beta (unstandardized)	Standard error	*T*-value	*P*-value (FDR-adjusted)
Neurobehavioral function				
Psychomotor speed/executive function	0.02	0.01	1.56	0.49
Verbal memory	0.01	0.01	1.05	0.59
Visual memory	−0.001	0.01	−0.10	0.92
Behavior/Mood	0.01	0.01	0.77	0.59
Volumetric measures				
Total gray matter volume	2206.29	543.07	4.06	0.001
Total cortical white matter volume	1137.01	647.51	1.76	0.17
Total subcortical gray matter volume	31.81	60.73	0.52	0.60
Right hippocampal volume	12.07	4.79	2.52	0.04
Left hippocampal volume	4.95	5.31	0.93	0.43
Volume of white matter hypointensities	−29.06	29.34	−0.99	0.43
CSF analytes				
t-tau	0.29	0.18	1.61	0.15
p-tau$_{181}$	−0.21	0.14	−1.46	0.15
Aβ_{1-42}	1.69	1.13	1.49	0.15
p-tau$_{181}$/t-tau	−0.01	0.004	−3.50	0.004
p-tau$_{181}$/Aβ_{1-42}	−0.0008	0.0004	−1.90	0.15

Three separate multivariate generalized linear models were performed to examine the effect of the Race x CHII interaction term on neurobehavioral variables, MRI-derived volumetric measures, and CSF analytes. All analyses controlled for age, years of education, WRAT-4 scores, body mass index (BMI), systolic blood pressure, history of diabetes, and APOE status (ε4 carriers vs. non-carriers). The MRI volumetric models also controlled for estimated intracranial volume. For neurobehavioral measures, lower scores are worse for all measures except for behavior/mood where higher scores are worse. Race is coded as 1 = Black and 0 = White. Abbreviations: FDR, false discovery rate; t-tau, total tau; p-tau, phosphorylated tau; Aβ, beta-amyloid.

scores, and BMI were associated with aspects of cognitive function, and systolic blood pressure correlated with right hippocampal volume. Years of education was not associated with any of the outcomes. When studying elite American football players, years of education might not be an adequate marker of SES as most play 4 years of college football. This was exemplified by the restricted range and lack of race group differences in education years in this sample. As a result of the DETECT study not being designed to examine racial disparities, detailed assessments of socioeconomic, language, cultural, and psychosocial history were not performed. There are thus many unmeasured variables related to racial identity that were not accounted for, which limit the validity of our findings and result in an incomplete understanding of the observed neurological racial disparities. Lower socioeconomic status, chronic health conditions and decreased health literacy (Verney et al., 2019), worse early-life education quality (Sisco et al., 2015) and fewer years of education (Weuve et al., 2018), perceived discrimination (Zahodne et al., 2017), geographical location (Liu et al., 2015), and genetic variations other than *APOE*ε4 (Lee et al., 2007; Logue et al., 2014; Mez et al., 2017a; Yu et al., 2017a,b) all contribute to increased vulnerability to cognitive decline among Black participants (Zahodne et al., 2017). These variables may have increased salience in American football players and thus have important clinical implications (Asken et al., 2016, 2017; Allison et al., 2018). Nuanced approaches (Galea et al., 2010) that model the multilevel interactions among social, environmental, genetic, and biological variables will elucidate racial heterogeneity associated with brain aging (in all settings).

A common explanation for the association between Black racial identity and neurological disorders is the higher rates of CVD risk factors (e.g., hypertension, diabetes, obesity) (Newman et al., 2005; Jackson et al., 2013; Barnes and Bennett, 2014; Benjamin et al., 2019) and cerebrovascular disease in Black participants (Zahodne et al., 2015; Graff-Radford et al., 2016; Filshtein et al., 2019). CVD is prevalent in former NFL players (Rogers et al., 2017) where it is a leading cause of mortality (Lehman et al., 2012, 2016; Lincoln et al., 2018). In this sample, Black participants had a higher BMI and higher systolic blood pressure. Yet, we observed effects after controlling for key CVD risk factors and there were minimal associations between the CVD risk factors and the outcomes. This could be related to imprecise measurement of adiposity and vascular health and/or the low rates of CVD. Additionally, racial disparities in CVD have been related to neighborhood conditions, access to and quality of medical care, and lifestyle behaviors, such as poor diet (Chin et al., 2011; Howard et al., 2018). These are variables that need to be included in future research to obtain a holistic understanding of racial disparities as it relates to CVD and brain aging, in general, and to CTE and related disorders, in particular.

Continued active engagement of Black participants in CTE-related research is encouraged to facilitate the study of various psychosocial, lifestyle, and genetic risk factors. Appropriate representation depends on the targeted football population being studied (e.g., active vs. former; college vs. NFL), given the changes of the racial make-up across levels of play and over time. The proportion of older adult (ages 40–69) former Black NFL players in this sample (i.e., 40%) is consistent with the rates of Black former NFL players reported in the mortality cohort studies of NFL players who played between 1959 and 1988 (Lehman et al., 2012, 2016). However, ∼70% of active NFL players today are Black (Lapchick and Marfatia, 2017; Lincoln et al., 2018). There are challenges and barriers to the recruitment, enrollment, and retainment of Black participants in research (Shavers et al., 2000; Braunstein et al., 2008; Byrd et al., 2011; Barnes et al., 2012; Barnes and Bennett, 2014), some of which may

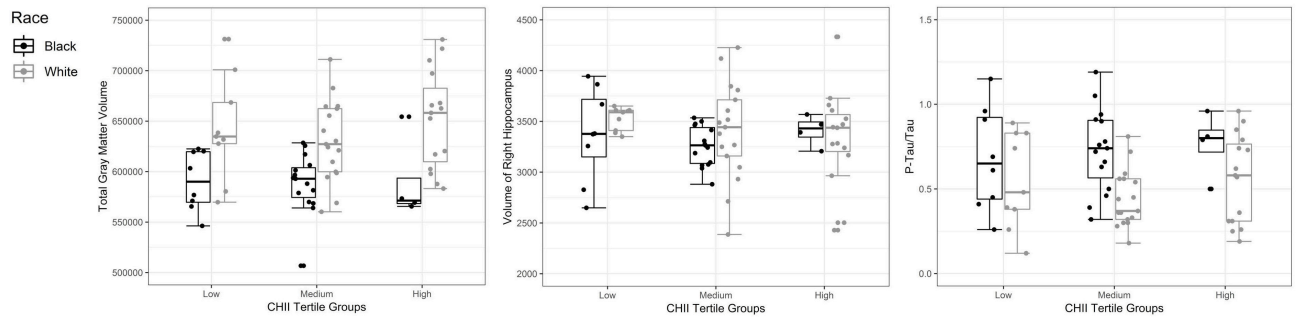

FIGURE 2 | Race by CHII Interaction Effects. Multivariate generalized linear models showed a significant Race × CHII interaction for the plotted outcomes. The x-axis are CHII score tertiles. The mid-point line in the box represents the median, the interquartile range box represents the middle 50%, and the whiskers represent the bottom and top 25% of data values. There was a statistically significant association between the Race by CHII interaction term with the respective outcomes after controlling for age, years of education, WRAT-4 scores, body mass index (BMI), systolic blood pressure, history of diabetes, and *APOE* status (ε4 carriers vs. non-carriers). Estimated intracranial volume was also included as a covariate for total gray matter volume and right hippocampal volume. Note that race group differences at each CHII group were not examined due to insufficient sample size.

have affected screening, selection, and retention of participants in this study. Progress has been made via methodological frameworks put forth by the National Institute on Aging's Health Disparities Framework (Hill et al., 2015) and recommendations provided by others (Barnes et al., 2012; Jefferson et al., 2013; Sabir and Pillemer, 2014; Samus et al., 2015; Brewster et al., 2018). Multipronged recruitment approaches anchored in establishing and maintaining trust of racially and ethnically diverse communities are advocated.

The generalizability of the findings is limited to symptomatic former NFL players and may not extend to other former NFL players, the broader American football population, or the general community. A complex system models approach (Galea et al., 2010) has been recommended (Brewster et al., 2018) to simultaneously evaluate the different variables and pathways that interact with self-identified race to influence neurological outcomes. This approach is computationally intensive and more suited to large multiple-source epidemiological datasets. The small sample size of the Black and White subgroups in this study additionally limits the ability to obtain reliable path estimates using statistical techniques such as structural equation modeling. Longitudinal research among large samples of former American football players (across all levels of play) are needed to validate our findings, elucidate race-moderated pathways of neurodegeneration and cognitive impairment, examine racial differences in trajectories of neurological outcomes, and identify the biopsychosocial variables that might contribute to observed race group differences. There were missing data across the different outcome variables, resulting in a reduced sample size and generalizability. Although the results remained largely similarly when the outcomes were analyzed based on complete data for that specific outcome (as opposed to complete data across all outcomes), there was some loss of statistical significance after restricting the sample to those who had complete data across all measures. Therefore, lack of statistical power may have precluded the ability to detect all associations. Unmeasured factors associated with missingness may have also affecting the accuracy of the estimated effects.

CONCLUSION

In this sample of symptomatic former NFL players, Black racial identity and RHI had an interactive effect on GMV, right hippocampal volume, and CSF p-tau$_{181}$/t-tau concentration. Although there were no statistically significant associations between exposure to RHI and these outcomes, Black participants had lower GMV, lower right hippocampal volume, and higher CSF p-tau$_{181}$/t-tau compared to White participants. Future investigations are needed to model the complex role(s) of social, economic, environmental, and genetic variables in the association among race, RHI, and neurological outcomes.

DATA AVAILABILITY STATEMENT

The dataset generated for this study is available on request to the corresponding author, as well as with the completion of a data use agreement.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by all study protocols were approved by the Boston University Medical Center Institutional Review Board. The Partners Institutional Review Board approved all neuroimaging procedures. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA, YT, AC, JJ, MMa, BS, and RS contributed to the study design and conception. MA, YT, AC, JJ, JM, MMa, OH, ÉF, BM, JP, IK, KG, NM, CL, MMu, AL, MC, OP, SB, MS, and RS

contributed to data acquisition, analysis, and interpretation of data. All authors have contributed to drafting and critically revising the manuscript. All authors have given final approval of the version to be published and agreed to be accountable for the work.

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SYSTEMATIC REVIEW
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Exploring Representation of Diverse Samples in fMRI Studies Conducted in Patients With Cardiac-Related Chronic Illness: A Focused Systematic Review

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Introduction/Purpose: Cardiovascular disease (CVD) is the leading cause of death worldwide, and in the United States alone, CVD causes nearly 840,000 deaths annually. Using functional magnetic resonance imaging (fMRI), a tool to assess brain activity, researchers have identified some brain-behavior connections and predicted several self-management behaviors. The purpose of this study was to examine the sample characteristics of individuals with CVD who participated in fMRI studies.

Methods: A literature search was conducted in PubMed, CINAHL, and Scopus. No date or language restrictions were applied and research methodology filters were used. In October 2017, 1659 titles and abstracts were identified. Inclusion criteria were: (1) utilized an empirical study design, (2) used fMRI to assess brain activity, and (3) focused on patients with CVD-related chronic illness. Articles were excluded if they: were theory or opinion articles, focused on mental or neuropathic illness, included non-human samples, or were not written in English. After duplicates were removed (230), 1,429 titles and abstracts were reviewed based on inclusion criteria; 1,243 abstracts were then excluded. A total of 186 studies were reviewed in their entirety; after additional review, 142 were further excluded for not meeting the inclusion criteria. Forty-four articles met criteria and were included in the final review. An evidence table was created to capture the demographics of each study sample.

Results: Ninety eight percent of the studies did not report the racial or ethnic composition of their sample. Most studies (66%) contained more men than women. Mean age ranged from 38 to 78 years; 77% reported mean age ≥50 years. The most frequently studied CVD was stroke (86%), while hypertension was studied the least (2%).

Conclusion: Understanding brain-behavior relationships can help researchers and practitioners tailor interventions to meet specific patient needs. These findings suggest that additional studies are needed that focus on populations historically underrepresented in fMRI research. Researchers should thoughtfully consider diversity

and purposefully sample groups by including individuals that are: women, from diverse backgrounds, younger, and diagnosed with a variety of CVD-related illnesses. Identifying and addressing these gaps by studying more representative samples will help healthcare providers reduce disparities and tailor interventions for all CVD populations.

Keywords: fMRI, cardiovascular disease, sample demographics, health disparities, chronic illness

INTRODUCTION

According to the World Health Organization, cardiovascular disease (CVD) is an umbrella term which includes a number of heart and blood vessel disorders. Disorders include cerebrovascular disease (stroke) and hypertension (World Health Organization). About 121.5 million Americans are living with some form of CVD, with direct and indirect costs of total cardiovascular diseases and stroke totaling more than $351.2 billion (Benjamin et al., 2018, 2019). CVD is currently the leading cause of death in the U.S., causing nearly 836,546 deaths annually (Benjamin et al., 2018, 2019). In addition to its high mortality rate, CVD is associated with other chronic illnesses, such as end-stage renal disease and diabetes (Liu et al., 2014; Leon and Maddox, 2015). Groups that differ by race, ethnicity, education level, gender, and socioeconomic status are negatively and disproportionately affected by CVD and other chronic illnesses, and trends show that the gaps in these disparities are widening (Di Chiara et al., 2015; Havranek et al., 2015; Singh et al., 2015; Mehta et al., 2016). Initiatives that target specific social determinants of health are needed (Valero-Elizondo et al., 2018).

Some CVD-related illnesses, such as hypertension, can be controlled with lifestyle modifications such as consistently eating a healthy diet, engaging in regular physical activity, and adhering to antihypertensive medication (Nicolson et al., 2004). Such activities are often referred to as self-management behaviors. To improve upon these self-management behaviors, and therefore reduce associated risks with CVD, more studies are needed to assist practitioners to better guide patients toward consistent healthy behaviors. As such, studies that link brain activity via functional magnetic resonance imaging to self-management behaviors may establish an important foundation in achieving desirable patient outcomes.

Functional magnetic resonance imaging, or fMRI, is a tool that measures brain activity by detecting changes in blood oxygenation and flow that correspond to neural activity (Devlin et al., 2007). The brain increases oxygen demand in areas that are more active, and to meet this demand, blood flow increases to the area. In previous studies, researchers have used fMRI to predict self-management behaviors, such as sunscreen use and smoking cessation (Falk et al., 2010, 2011). Falk et al. (2010) measured neural activity in the medial prefrontal cortex (MPFC) of the brain while people watched persuasive messages about the value of using sunscreen regularly (Falk et al., 2010). They used these measurements to predict whether individuals would increase their sunscreen use, above and beyond self-report. They found that activity in the MPFC was significantly related to persuasion-induced behavior change, or increased sunscreen use, over the course of two weeks (Falk et al., 2010).

A subsequent study looked at the same area of the brain (MPFC) and tested whether neural activity in response to messages promoting smoking cessation could predict smoking cessation, above and beyond self-report (Falk et al., 2011). The researchers found that increases in MPFC activity were associated with decreases in expired carbon monoxide following exposure to professionally developed quitting ads (Falk et al., 2011). In both studies, by measuring MPFC activity while subjects viewed the persuasive messages, the researchers were able to predict the behavioral efficacy of the messages "above and beyond what participants' own self-reported attitude and intention change could predict" (Falk et al., 2010, 2011).

Other studies have examined the antagonistic relationship between analytic and socio-emotional neuroprocessing. Jack et al. (2013) found that individuals who were better able to process both analytic and socioemotional prompts, were better able to make plans, and act on the plans that they had developed (Jack et al., 2013). The analytic network, also known as the task positive network, pertains to skills, problem solving, and goal-directed actions (Duncan and Owen, 2000; Jack et al., 2013). Thus, it is activated by attention-demanding tasks (Fox et al., 2005; Uddin et al., 2009; Bressler and Menon, 2010). By contrast, the empathetic network, also referred to as the default mode network, encompasses emotional management and self-awareness, and is activated during periods of wakeful rest (Denny et al., 2012; Eisenberger and Cole, 2012; Marstaller et al., 2016).

Analytic information and emotional information are processed in different areas of the brain and are anti-correlated (Jack et al., 2013). The analytic information is processed in prefrontal and parietal areas of the brain, while the emotional information is processed in the posterior cingulate and medial prefrontal cortices (Duncan and Owen, 2000; Fox et al., 2005). This means that responses to different types of information varies depending on individual characteristics (Singh et al., 2015). One study reported findings that socio-emotional processing was positively associated with sharing of health information with others (Jones et al., 2019). Better understanding how the brain processes different types of information will help to develop individualized, and potentially more effective self-management interventions.

The purpose of this systematic review was to examine the demographic characteristics presented in fMRI studies that have been conducted with patients with CVD-related illnesses. Specifically, we aimed to evaluate studies on brain activity in participants with CVD to determine which patient populations the findings were applicable to. Results from the studies reviewed

in this paper can be used to guide future studies to explore brain activity patterns to predict specific behaviors. For example, fMRI studies that focus on patients with CVD would be useful in helping researchers and clinicians better understand how brain activity patterns can be used to predict self-management of CVD, and which interventions may be more useful to individuals with certain patterns of brain activity (Moore et al., 2019).

METHODS

Team

The team that conducted this work consisted of a doctorally-prepared nurse scientist, a health sciences librarian, and four undergraduate students. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used to guide reporting for this review.

Search Strategy

The databases PubMed, CINAHL, and Scopus were searched on October 2, 2017 to retrieve articles on use of functional magnetic resonance imaging (fMRI) in populations with chronic illnesses (see **Appendix A**). Controlled vocabulary (i.e., Medical Subject Headings and CINAHL Headings) and keywords were used to identify related terms for chronic illness and functional magnetic resonance imaging (fMRI). No date or language restrictions were applied to the search. In order to limit retrieval to treatment and diagnostic studies that contain empirical evidence, therapy, and diagnosis research methodology filters were used in PubMed and adapted for use in CINAHL and Scopus (Lokker et al., 2011). A total of 1,659 titles and abstracts were identified for review.

Study Selection

Two reviewers from the study team independently assessed study eligibility using Covidence systematic review software [Covidence Systematic Review Software]. Studies were selected for further review if they met the following criteria: (1) utilized an empirical study design, (2) used fMRI to assess brain activity, and (3) focused on patients with CVD-related chronic illness.

Articles were excluded that were not original research (e.g., theory or opinion articles), focused on mental or neuropathic illness, included non-human samples, or were not written in English.

Search Results

The search strategies retrieved a total of 1,659 articles. After the removal of duplicates, 1,429 articles remained for screening, of which 1,243 were excluded at the title and abstract level. Following a full-text review of 186 articles, 142 were excluded for not meeting criteria. Forty-four articles were included in the final review (see **Figure 1** for a flow diagram).

Presentation of Results

A table that categorized the studies based on geographical location was created to examine the variety of settings in which the studies had been conducted (see **Table 1**). Another table was developed to provide brief quantitative and descriptive summaries of the studies' design, gender distribution, mean age, and brain regions of interests (see **Table 2**). Lastly, a third table was created to determine which demographic characteristics (race, age, gender, income, and education) were examined in each study sample (see **Table 3**). The studies were categorized by the first author's last name and year, the chronic illness being studied, and the number of participants in each sample.

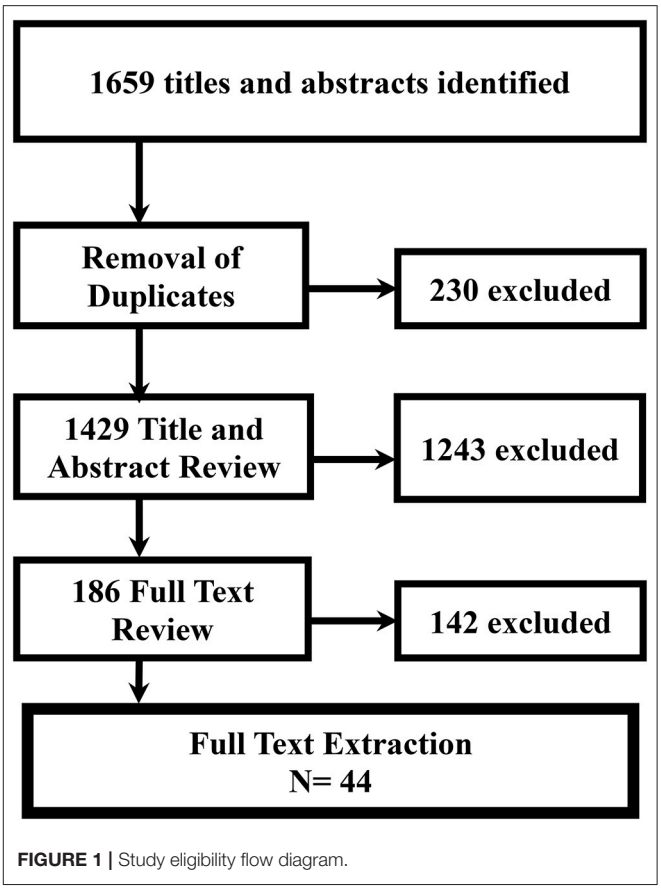

FIGURE 1 | Study eligibility flow diagram.

RESULTS

Cardiovascular-Related Diseases

There were 38 studies that focused on patients that had strokes (86%) (Pineiro et al., 2001; Carey et al., 2002; Kato et al., 2002; Schaechter et al., 2002, 2007; Kimberley et al., 2004; Luft et al., 2004a,b, 2008; Tombari et al., 2004; Kim et al., 2006; Kwon et al., 2007; Shin et al., 2008; Takahashi et al., 2008; Fair et al., 2009; Menke et al., 2009; von Lewinski et al., 2009; Meehan et al., 2011; Michielsen et al., 2011; Rijntjes et al., 2011; Szaflarski et al., 2011; Whitall et al., 2011; Deng et al., 2012; Kononen et al., 2012; Veverka et al., 2012, 2014; Lazaridou et al., 2013; Pinter et al., 2013; Ramos-Murguialday et al., 2013; Sun et al., 2013; Brownsett et al., 2014; Hodgson et al., 2014; Mattioli et al., 2014; Milot et al., 2014; Rehme et al., 2015; Kielar et al., 2016; Landsmann et al., 2016; Pelicioni et al., 2016). Of the 38 stoke studies, the majority (84%) of the studies were randomized controlled trials (see **Table 2**). Four cohort studies (9%) had participants with chronic kidney disease (Lux et al., 2010; Jahanian et al., 2014; Zhang et al., 2015; Li et al., 2016). One cohort study had participants who had been diagnosed with type 2 diabetes (2%)

and one cohort study had participants who had been diagnosed with hypertension (2%) (Gold et al., 2005; He et al., 2015).

Race, Ethnicity, and Geographic Location

The vast majority of studies (98%) did not report the racial or ethnic composition of the sample (**Table 3**). In the one study that did examine race, the report stated that over half of the participants were "Black," followed by "White" participants, and a small percentage of "Hispanic/Other" participants (Luft et al., 2008). Most of the stroke studies were conducted in the United States (**Table 1**). Half of the renal studies were conducted in China. The type 2 diabetes study was conducted in China. The hypertension study was conducted in the United States. See **Table 1** for additional details on where the studies were conducted.

TABLE 1 | Geographic location.

Chronic illness	Location	# of studies
Stroke	USA	15
	Germany	4
	Korea	3
	United Kingdom	3
	Austria	2
	Canada	2
	Czech Republic	2
	Brazil	1
	China	1
	Finland	1
	France	1
	Italy	1
	Japan	1
	Netherlands	1
CKD/ESRD	China	2
	Germany	1
	USA	2
Type 2 DM	China	1
HTN	USA	1

CKD, chronic kidney disease; ESRD, end-stage renal disease; DM, diabetes mellitus; HTN, hypertension.

Age

The majority (95%) of the studies provided the age of the participants (**Table 3**). There was variation in the manner which age was presented in each study. Some studies provided an overall mean for all of the participants, while others reported means for the intervention or affected groups compared to the control or "healthy" groups. The mean age of the participants ranged from 34 to 73 years; 77% of the studies reported mean age $\geq$50 years.

Gender

The majority (91%) of the studies reported the gender distribution of the sample. Most studies (66%) contained more men than women (**Table 2**). When examining the samples by chronic illness, studies focused on stroke patients had more men than women. Studies of chronic renal patients had more men than women. The study of patients with type 2 diabetes had more men than women, while the study of participants with hypertension had more women than men.

Income

None of the studies included in this review presented information on the participants' income.

Education

A total of 10 studies (23%) provided information on the participants' education levels, overall (**Table 3**). In terms of stroke studies specifically, six out of 38 studies (16%) reported on the education of participants. The mean years of education ranged from 6 to 16.8 years for five of the studies. An additional study

TABLE 2 | Summary of studies.

Chronic illness	# of studies	Study design		Mean age (years)		Gender distribution	Brain regions of interest
Stroke	38	32 RCTs	6 cohort	Lowest mean age reported: 40 (range = 34,67)	Highest mean age reported: 73 (SD = 4)	Males > females	• Areas of chronic diaschisis or peristroke areas • Primary motor cortex • Perilesional tissue • Supplementary motor area • Posterior cerebellar lobe
CKD/ESRD	4		4 cohort	Lowest mean age reported: 34 (SD = 7)	Highest mean age reported: 72 (SD = 7)	Males > females	• Default mode network • Hippocampus • Frontal and parietal lobes • Bilateral inferior frontal gyrus • Right superior temporal gyrus
Type 2 diabetes	1		Cohort	41 (range = 31, 53)		Males > females	• Anterior cingulate cortex • Bilateral DLPFC
Hypertension	1		Cohort	67 (SD = 8.9)		Males < females	• Frontal and medial • Temporal lobes

CKD, chronic kidney disease; ESRD, end-stage renal disease; RCT, randomized controlled trial.

TABLE 3 | Study characteristics.

References	Chronic illness	# of participants	Demographic characteristic reported				
			Race	Age	Gender	Income	Education
Brownsett et al. (2014)	Stroke	16	−	+	+	−	+
Carey et al. (2002)	Stroke	10	−	+	+	−	−
Deng et al. (2012)	Stroke	16	−	+	+	−	−
Fair et al. (2009)	Stroke	6	−	−	−	−	−
Gold et al. (2005)	Hypertension	54	−	+	−	−	−
He et al. (2015)	Type 2 diabetes	24	−	+	+	−	+
Hodgson et al. (2014)	Stroke	16	−	+	+	−	+
Jahanian et al. (2014)	CKD	20	−	+	+	−	−
Kato et al. (2002)	Stroke	11	−	+	+	−	−
Kielar et al. (2016)	Stroke	38	−	+	+	−	+
Kim et al. (2006)	Stroke	18	−	+	+	−	−
Kimberley et al. (2004)	Stroke	16	−	+	+	−	−
Kononen et al. (2012)	Stroke	11	−	+	+	−	−
Kwon et al. (2007)	Stroke	31	−	+	+	−	−
Landsmann et al. (2016)	Stroke	24	−	+	+	−	+
Lazaridou et al. (2013)	Stroke	17	−	−	−	−	−
Li et al. (2016)	ESRD	51	−	+	+	−	+
Luft et al. (2008)	Stroke	71	+	+	+	−	−
Luft et al. (2004a)	Stroke	21	−	+	+	−	−
Luft et al. (2004b)	Stroke	28	−	+	+	−	−
Lux et al. (2010)	ESRD	24	−	+	+	−	+
Mattioli et al. (2014)	Stroke	12	−	+	+	−	+
Meehan et al. (2011)	Stroke	18	−	+	+	−	−
Menke et al. (2009)	Stroke	8	−	+	+	−	−
Michielsen et al. (2011)	Stroke	40	−	+	+	−	−
Milot et al. (2014)	Stroke	20	−	+	+	−	−
Pelicioni et al. (2016)	Stroke	21	−	+	+	−	−
Pineiro et al. (2001)	Stroke	28	−	+	+	−	−
Pinter et al. (2013)	Stroke	7	−	+	−	−	−
Ramos-Murguialday et al. (2013)	Stroke	32	−	+	+	−	−
Rehme et al. (2015)	Stroke	21	−	+	+	−	−
Rijntjes et al. (2011)	Stroke	12	−	+	+	−	−
Schaechter et al. (2007)	Stroke	7	−	+	+	−	−
Schaechter et al. (2002)	Stroke	4	−	+	+	−	−
Shin et al. (2008)	Stroke	14	−	+	+	−	−
Sun et al. (2013)	Stroke	18	−	+	+	−	−
Szaflarski et al. (2011)	Stroke	8	−	+	+	−	+
Takahashi et al. (2008)	Stroke	13	−	+	+	−	−
Tombari et al. (2004)	Stroke	18	−	+	+	−	−
Veverka et al. (2014)	Stroke	14	−	+	+	−	−
Veverka et al. (2012)	Stroke	14	−	+	+	−	−
von Lewinski et al. (2009)	Stroke	9	−	+	+	−	−
Whitall et al. (2011)	Stroke	111	−	+	+	−	−
Zhang et al. (2015)	ESRD	46	−	+	+	−	+

CKD, chronic kidney disease; ESRD, end-stage renal disease.

reported that four of its participants received 14–17 years of education, however, no education data was available for the remainder of the participants. With regards to chronic kidney disease, three out of the four studies (75%) reported on the education of participants. The mean education ranged from 11.4 to 13.1 years. Regarding the sole type 2 diabetes study, mean participant education was reported as 9.8 years. Lastly, the singular hypertension study included in this review did

not include information with respect to years of education of participants.

DISCUSSION

The objective of this study was to examine the sample characteristics of individuals with CVD who participated in fMRI studies. A total of 44 studies were included in the review. Our findings demonstrate that race and ethnicity and socioeconomic status of participants are not often considered, as demonstrated in the inconsistency in reporting demographic characteristics from across the studies. This review highlights the need for more stringent and detailed collection of demographic data from participants enrolled in fMRI studies. Additional reviews are needed that evaluate fMRI studies sample sizes and stricter statistical threshold. Future studies are needed that focus on populations that have been historically underrepresented in fMRI/CVD-related research. Only one study mentioned the racial or ethnic composition of participants. Additionally, in 66% of the studies, the majority of participants were male. By studying a sample that is more representative of the general population and by expanding the type of CVD studied, researchers can identify practices that are relevant for populations that are disproportionately impacted by hypertension, such as African Americans. Diverse populations (i.e., racial and ethnic, gender, and age groups) vary greatly with respect to health risks such as CVD, as well as access to health care and other health disparities (Leigh et al., 2016). Patients with lower incomes and education levels may increased CVD risk (Marshall et al., 2015; Khaing et al., 2017). Additional research is needed to explore differences in brain activity patterns and related behaviors among diverse patients with CVD.

Of the studies identified as having reported CVD-related outcomes, 84% examined stroke, while only 2% examined hypertension or type 2 diabetes. It is important to note that understanding brain-behavior relationships has the potential to help researchers and practitioners tailor interventions to meet specific patient needs. These points further demonstrate a need for additional studies that use fMRI to better understanding brain-behavior relationships among patients with specific CVD-related diseases.

LIMITATIONS

The primary limitation of this study was the variety in reporting of demographic characteristics across the studies. As a result, it limited the summaries and conclusions that could be made. However, this lack of reporting supports the idea that future fMRI research needs to consider and prioritize racial/ethnic background, income, and education during the recruitment and sampling process. Additionally, the original goal of this literature review was to examine the fMRI studies that had be conducted with participants who self-identified as African American and were diagnosed with hypertension. Given that only one study met these criteria, the search strategy was expanded to include studies with conditions associated with hypertension (stroke, ESRD, diabetes). Given the large number of stroke studies in this review, a meta-analysis of these studies would be an interesting contribution to the literature.

CONCLUSION

This review suggests that certain groups with CVD disease (women, younger adults, racial/ethnicity minorities) are underrepresented in fMRI research. Therefore, there is a knowledge gap with respect to evidence about brain-behavior connections in groups that are of different races, ethnicities, or genders. Researchers should consider diversity when selecting sampling methods to include individuals from underrepresented groups, such as: women, individuals from diverse backgrounds, younger adults (age <50 years), and those diagnosed with hypertension. When recruiting participants with CVD for fMRI studies, researchers need to consider barriers that prevent these populations from participating, such as socioeconomic status, distrust of the scientific community, cultural barriers, and lack of knowledge related to fMRI research. Identifying and addressing these gaps will lead to the reduction of disparities in fMRI research and improve interventions for all CVD populations.

AUTHOR CONTRIBUTIONS

We are pleased to submit this manuscript, entitled Exploring Representation of Diverse Samples in fMRI Studies Conducted in Patients with Cardiac-Related Chronic Illness: A Focused Systematic Review to be considered for publication. This paper highlights findings of a focused review on the demographics of patients with cardiovascular disease who participated in fMRI studies. This manuscript has not been published and is not under submission elsewhere. There are no conflict of interests that exist. All authors contributed substantively to the content of this manuscript and are in agreement for its readiness to be considered for publication: LJ and EG: development/implementation of methods, study review, and manuscript preparation. JD, JE, CR, and BG: manuscript preparation. JH: study review and manuscript preparation. RR-S: implementation of methods and manuscript preparation. ET and CS: implementation of methods, study review, and manuscript preparation.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX A

Search Strategies by Database

PUBMED

#1. ("fMRI" OR "functional magnetic resonance imaging" OR "functional MRI" OR (("brain imaging" OR neuroimag*) AND functional) OR neuroprocess*).
#2. ("Chronic Disease"[Mesh] OR chronically OR chronic).
#3. ((sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnose[Title/Abstract] OR diagnosed[Title/Abstract] OR diagnoses[Title/Abstract] OR diagnosing[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnostic[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) OR ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])).
#4. #1 AND #2 AND #3.

CINAHL

S1. ("fMRI" OR "functional magnetic resonance imaging" OR "functional MRI" OR (("brain imaging" OR neuroimag*) AND functional) OR neuroprocess*).
S2. (MH "Chronic Disease" OR chronically OR chronic).
S3. ((TI sensitiv* OR AB sensitiv* OR MH "Sensitivity and Specificity" OR TI diagnose OR AB diagnose OR TI diagnosed OR AB diagnosed OR TI diagnoses OR AB diagnoses OR TI diagnosing OR AB diagnosing OR TI diagnosis OR AB diagnosis OR TI diagnostic OR AB diagnostic OR MH "Diagnosis" OR MH "Diagnostic Imaging" OR MH "Diagnostic Services" OR MH "Diagnostic Errors" OR MH "Diagnosis, Differential" OR MW DI) OR (((TI clinical OR AB clinical) AND (TI trial OR AB trial)) OR MH "Clinical Trials+" OR TI random* OR AB random* OR MH "Random Assignment" OR MW TH)).
S4. S1 AND S2 AND S3.

SCOPUS

#1. TITLE-ABS-KEY("fMRI" OR "functional magnetic resonance imaging" OR "functional MRI" OR (("brain imaging" OR neuroimag*) AND functional) OR neuroprocess*).
#2. TITLE-ABS-KEY (chronic OR chronically).
#3. TITLE-ABS-KEY (cardiovascular OR CVD OR heart OR circulatory OR myocardial OR myocardium OR "blood vessel" OR hypertension OR hypertensive OR "blood pressure").
#4. ALL(sensitiv* OR Specificity OR diagnose OR diagnosed OR diagnoses OR diagnosing OR diagnosis OR diagnostic OR (clinical AND trial*) OR random* OR "therapeutic use").
#5. #1 AND #2 AND #3 AND #4.

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MINI REVIEW
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Racial Differences in Dietary Relations to Cognitive Decline and Alzheimer's Disease Risk: Do We Know Enough?

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The elderly population in the US is increasing and projected to be 44% minority by 2060. African Americans and Hispanics are at increased risk of cognitive impairment and Alzheimer's disease compared to non-Hispanic whites. These conditions are associated with many other adverse health outcomes, lower quality of life, and substantial economic burden. In the past few decades, diet has been identified as an important modifiable risk factor for cognitive decline and Alzheimer's disease. Some studies report poor diet quality among African American and Hispanic older adult populations compared to their white counterparts. We have a limited understanding of how diet affects brain health in different racial-ethnic groups. One primary reason for our lack of knowledge is that most cohort studies are of majority non-Hispanic white participants. Moreover, those that do include minority participants do not publish their findings stratified by racial-ethnic groups, and likely have a less accurate measurement of dietary intake among minority groups. In this review, we summarize the current, albeit limited, literature on racial/ethnic differences in dietary relations to dementia outcomes. We will also discuss methodological issues in conducting nutrition studies in diverse cultures, and suggestions for future research directions. Overcoming the gaps will make it possible to make dietary recommendations for Alzheimer's prevention that are more relevant for different racial/ethnic groups and set us on a faster track to reduce health disparities.

Keywords: diet, nutrition, cognition, health disparities, race

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INTRODUCTION

Currently, around 5.7 million Americans have Alzheimer's dementia, and with a growing aging population, the number is projected to increase to 13.8 million by 2050 (Hebert et al., 2013; Alzheimer's Association, 2018). The US aging population is also expected to become more racially and ethnically diverse in the coming years, so that by the year 2060, it will be approximately 44% minority (Colby and Ortman, 2014). One systematic review of multi-ethnic cohort studies concluded that dementia incidence rates are higher in African Americans and Hispanics compared to non-Hispanic Whites (Mehta and Yeo, 2017). Some have argued that these observed disparities are due to a multitude of related factors, including increased prevalence of cardiovascular conditions, lower education and socioeconomic status, barriers to health care, and certain lifestyle

factors (Judd et al., 2013; Diaz-Venegas et al., 2016; Howard et al., 2018; Weuve et al., 2018). With limited treatments to reverse memory loss or dementia, the identification of modifiable risk factors are of great public health interest. Diet has emerged as a modifiable factor that affects cardiovascular-related conditions but also may have independent effects on the development of dementia. A large body of literature has found that healthy dietary patterns, including the Mediterranean (Scarmeas et al., 2009; Tangney et al., 2011; Koyama et al., 2015; Morris et al., 2015b; Bhushan et al., 2018), DASH (Dietary approach to Reduce Hypertension) (Tangney et al., 2014; Morris et al., 2015b) and MIND (Mediterranean-Dash Intervention for Neurodegenerative Diseases) diets (Morris et al., 2015b,c; Berendsen et al., 2018), and specific foods [e.g., berries (Devore et al., 2012; Agarwal et al., 2019), vegetables (Morris et al., 2006, 2018; Ye et al., 2013a), fish (Morris et al., 2003; Samieri et al., 2018)] and nutrients [vitamin E (Morris et al., 2002a; Beydoun et al., 2015), flavonoids (Devore et al., 2012; Holland et al., 2020), B vitamins (Morris et al., 2005), unsaturated fats (Morris et al., 2004)] are associated with slower cognitive decline and/or reduced risk of dementia. However, the generalizability of these findings to individuals of different race and ethnic backgrounds is not well characterized. We know that diet quality varies by race and ethnicity in the U.S., but differences also occur by socioeconomic status, the region of the country, and urban/rural settings (Aggarwal et al., 2012; Hiza et al., 2013; McInerney et al., 2016; Bloom et al., 2017; Lee-Kwan et al., 2017). Racial/ethnic disparities in dementia may be due, in part, to dietary intakes of the nutrients and foods found to be important to brain health. This was reported to be the case for higher incidence rates of stroke and hypertension among African Americans compared to whites, which were partially explained by higher consumption of a Southern westernized diet pattern among African Americans (Judd et al., 2013; Howard et al., 2018). Unfortunately, in our current state of knowledge, there is limited data to investigate to what extent diet may account for these disparities in dementia. In this review, we will characterize social and biological differences by race and ethnicity that influence diet quality and nutritional metabolism, describe the existing multi-racial/ethnic studies of diet and dementia, and identify the methodological challenges and future directions in closing the gap in this field of scientific inquiry. The existing studies on the association between dietary patterns/food groups/nutrients and cognitive decline/Alzheimer's dementia risk from the longitudinal cohorts of US adults that included multi-racial/ethnic groups with more than 20% minority population are discussed in this review.

RACIAL/ETHNIC DIFFERENCES IN HEALTH

Various social and demographic factors that have been studied for health disparities in Alzheimer's dementia include educational attainment (Weuve et al., 2018), bilingualism (Lamar et al., 2019), neighborhood greenness (Brown et al., 2018), and stressful life events (Zuelsdorff et al., 2020). Similar social and economic aspects may also affect the diet quality by race, including education and income (Raffensperger et al., 2010), health literacy (Kuczmarski et al., 2016), food prices and diet costs (Townsend et al., 2009) and neighborhood grocery store availability (Powell et al., 2007; Bower et al., 2014). Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study reported lower nutrient-based diet quality among African Americans compared to whites and found health literacy and education as important predictors of diet quality in this urban population (Raffensperger et al., 2010; Kuczmarski et al., 2016). Similarly, African Americans in the Jackson Heart Study reported fast-food clusters (including fast foods, salty snacks, non-diet soft drinks, and meat), as the most common dietary pattern in the study population and was found to be associated with significantly lower levels of plasma carotenoids and alpha tocopherols (Talegawkar et al., 2008). Considering that different social, economic, and demographic factors may influence both diet quality and cognition, examining racial differences in the association of diet with Alzheimer's dementia and/or cognitive decline, may help us explain, at least in part, health disparities in Alzheimer's dementia and related disorders.

Although race is socially constructed with little to no basis in biology, there are non-observable differences in nutritional metabolism based on such factors as skin color and body composition (Hall et al., 2010; Bhupathiraju et al., 2011). For example, ultraviolet rays are absorbed by the skin at different rates depending on the level of melanin or pigment in the skin. Racial groups with darker skin pigment require greater sun exposure than lighter-skinned groups to synthesize the same amount of vitamin D (Hall et al., 2010; Gallagher et al., 2013). Differences among racial/ethnic groups in fat and lean body mass can affect the storage and metabolism of a number of vitamins and minerals (Morton et al., 2003; Lear et al., 2009; Travison et al., 2011; Santoro et al., 2018). In the feeding trials, African Americans reported higher, postprandial triglycerides (Goff et al., 2016) and subnormal ghrelin (a gut-brain peptide to signal hunger) suppression (Brownley et al., 2004) compared to Whites. Independent of obesity, body fat distribution, and behavioral factors, African Americans but not Hispanics have high insulin resistance compared to non-Hispanic Whites (Haffner et al., 1996). Genetic variations can also affect susceptibility to DNA damage and DNA repair. For example, African Americans are reported to have lower serum levels of antioxidant nutrients in comparison to whites, yet surprisingly have less oxidative damage to DNA (Huang et al., 2000; Watters et al., 2007). Similarly, a longitudinal analysis indicated higher parathyroid hormones increased diabetes risk only in Whites and not in African Americans (Reis et al., 2016). The growing evidence of differences in nutrition metabolism by race and ethnicity is a compelling reason for their scientific exploration in the dementia field.

MULTI-RACIAL/ETHNIC COHORT STUDIES ON DIET AND DEMENTIA

A large body of literature over the past two decades has established diet as an important modifiable risk factor for

dementia in older populations. Various healthy dietary patterns [e.g., Mediterranean (Aridi et al., 2017), DASH (Tangney et al., 2014), MIND (Morris et al., 2015c)], foods (Morris et al., 2006, 2016, 2018; Devore et al., 2012; van de Rest et al., 2016; Samieri et al., 2018) and nutrients (Morris et al., 2002a,b, 2003, 2004, 2005, 2018; Haan et al., 2007; Moorthy et al., 2012; Beydoun et al., 2018b; Schneider et al., 2018) have been associated with slower cognitive decline and lower dementia risk in prospective cohort studies. The healthy dietary pattern may exert a neuroprotective effect by reducing oxidative stress and inflammation (Bagetta et al., 2020) and was found to be associated with less brain atrophy (Gu et al., 2015). These dietary patterns are plant-based consisting of foods such as fruits, berries, vegetables, leafy greens, whole grains, fish, olive oil, legumes, and nuts. These foods are rich in essential nutrients as well as bioactive that have anti-inflammatory and antioxidant properties (Ellis et al., 2011; Alvarez-Suarez et al., 2014; Giampieri et al., 2014). *In vitro* and *in vivo* evidence indicate that bioactive and some of their metabolites can cross the blood-brain barrier (Youdim et al., 2003, 2004) and through signal transduction cascades may directly act on neurons and glia (Jaeger et al., 2018). Animal studies reported berries and leafy greens improve cognitive function via increased neurogenesis, and insulin-like growth factor-1 signaling, and reversed neuronal aging by reducing oxidative stress (Joseph et al., 1998; Shukitt-Hale et al., 2015; Elkhadragy et al., 2018). Additionally, these dietary patterns also limit the consumption of red meat, fatty foods, and sweets. Another set of evidence indicate the high fat/cholesterol diet's deleterious effect on cognition via its effect on synaptic integrity, increased hippocampal insulin resistance, inflammation (Arnold et al., 2014; Denver et al., 2018), as well as increased levels of amyloid precursor protein (Thirumangalakudi et al., 2008).

The association of diet with cognitive decline and Alzheimer's dementia risk has emerged as important factor that may have huge public health impact on aging population. However, there is a paucity of information on how these associations may differ by race or ethnicity. Two primary reasons emerge to explain this gap. First, not all cohort studies include diet assessment, and those that do are almost exclusively of non-Hispanic white populations. Second, the few multi-racial/ethnic cohort studies that include diet rarely report the findings stratified by racial/ethnic groups (Koyama et al., 2015; Beydoun et al., 2018b), although some report p-values for tests of interaction of the findings by these groups as discussed below.

Table 1 summarizes the findings from nine multi-racial/ethnic cohort studies in the US that report diet associations with dementia outcomes. The studies are large, ranging from 1,956 to 18,080 participants, and the percentages of minority participants provide sufficient sample sizes to observe most diet associations with the outcomes (percentages of minority groups range from 22 to 100%). The non-white groups represented in these studies are African American and Puerto Rican. There is limited (Ye et al., 2013a,b) or non-existent data for Mexican, Native American, and Asian populations. The findings of studies on African Americans and Puerto Ricans cannot be assumed to apply to these other racial/ethnic groups as there are large cultural and social differences, including dietary practices.

As shown in **Table 1**, the multi-racial/ethnic cohort studies have a number of positive findings for dementia outcomes and nutrients (vitamin E, vitamin D, folate, vitamin B12, dietary fats), foods (vegetables, fish, caffeine, alcohol), and diet patterns. Some of the studies provide no information about whether the findings were analyzed by race/ethnicity (McEvoy et al., 2019), but in those that do, the findings are not stratified by racial/ethnic group. This is most likely because in nearly every case, tests for interaction effects by race/ethnicity are not statistically significant, although there are a few exceptions. The Health, Aging and Body Composition Study (Health ABC) reported a protective association of the Mediterranean diet with slower cognitive decline in African American but not in whites (Koyama et al., 2015), and a cross-sectional study from the HANDLS (Beydoun et al., 2018b) found a positive association of dietary vitamin D and better visual memory in whites but not in African American. Even though most of these studies did not find statistically significant differences by race or ethnicity, the possibility of heterogeneous effects of diet on brain health by race remains. As discussed below, one must question whether dietary behaviors among the minority participants have been well characterized in these studies.

METHODOLOGICAL ISSUES

It is not enough to implement a standardized diet questionnaire into a multi-racial/ethnic cohort study and expect to elicit valid findings on diet and dementia by racial/ethnic groups. The diet assessment tool must represent the foods, cooking methods, recipes and portion sizes that are relevant to the population under study. For diet assessment tools, one size does not fit all. Food frequency questionnaires (FFQ) are the primary method of diet assessment in large epidemiological studies of chronic conditions. They provide a measure of long-term intake that is most relevant to conditions with long latency. This is in contrast to other methods, such as biochemical measures or 24-h dietary recall and diet recording, that may not be good representations of more habitual diet, particularly those nutrients that have high day-to-day variability (Willett, 2013). Although FFQs have been used as a valid and reproducible tool of dietary intake for many years, they are not generalizable beyond the populations for which they have been developed. This is particularly true for racial/ethnic groups as most FFQs were developed for non-Hispanic white populations. FFQs have a predefined list of food items, to which participants respond regarding usual frequency of intake, and for some FFQs, usual portion size (e.g., small, medium, large). The list of foods and their corresponding frequencies and portion sizes vary among FFQs. Two FFQs that have been widely adopted for use by many of the cohort studies are those developed by Willett et al. (1985) (used in the Nurses' Health Study and Health Professional Follow-up Study) and Block et al. (1986) (used in the National Health and Nutrition Examination Survey, or NHANES). Both the

TABLE 1 | Summary of studies on association of Dietary Patterns with cognitive decline or Incident AD that have at least > 20% minority population included.

Cohort and study population	Minority population%	Years Follow-up	N; Mean Age (*SD*)	Exposure	Outcome	Findings	Exposure Interaction with Race
WHICAP- Washington Heights-Inwood Columbia Aging Project (Multi-racial) 68% Female	African American (34%) and Hispanics (34%)	Longitudinal, 4–5 years	*N* = 2258; 77.6 (6.6)	Mediterranean diet	Incident MCI Progression of MCI to AD	↓ MCI risk and ↓ risk for MCI conversion to AD (Scarmeas et al., 2009)	Not reported
				Healthy dietary pattern for study population *	Incident AD	↓ AD risk (Gu et al., 2010)	*No stratified analysis by race*
				Total calories and Fat intake	Incident AD	↑ AD risk (Luchsinger et al., 2002)	
				Antioxidant vitamin	Incident AD	No association (Luchsinger et al., 2003)	
CHAP-Chicago Health and Aging Project	African American (63%)	Longitudinal, 6–9 years	*N* = 3790; 75.4 (6.2)	Mediterranean diet, HEI-2005	Cognitive decline OR Incident AD	Mediterranean diet ↓cognitive decline (Tangney et al., 2011)	Diet*race not significant *No stratified analysis by race*
				Fruits and Vegetables		Vegetable intake ↓ cognitive decline (Morris et al., 2006)	Diet*race not significant
				Fish intake		n-3 FA ↓ AD risk (Morris et al., 2003)	Diet*race not significant
				Antioxidant vitamins		Vitamin E from foods ↓ cognitive decline (Morris et al., 2002b) ↓ AD risk (Morris et al., 2002a)	Diet*race not significant
				Folate Vitamin B12		↑ Cognitive decline (Morris et al., 2005) ↓ Cognitive decline (Morris et al., 2005)	Diet*race not significant
				Dietary fats		Saturated fats ↑cognitive decline (Morris et al., 2004)	Animal fat*race was not significant.
				Serum Vitamin B12		↓ Cognitive decline (Tangney et al., 2009)	Vitamin B12* race was not significant
				Homocysteine		No association	Homocysteine* race was not significant
				Methyl malonic acid		↑ Cognitive decline (Tangney et al., 2009)	Methyl malonic acid* race was not significant.
Health ABC – Health Aging and Body Composition Study (Biracial)	African American (38%)	Longitudinal, 8.0 years	*N* = 2326; 74.6 (2.9)	Mediterranean diet	Cognitive decline	↓ Cognitive decline in Blacks not Whites (Koyama et al., 2015)	Mediterranean diet*race was significant *Stratified analysis by race*
Health and Retirement study 60% women	African American (22%)	Cross-sectional	*N* = 5907; 68 (10.8)	Mediterranean diet	Cognitive Scores	" + " Cognition (McEvoy et al., 2017)	Not reported
				MIND diet		" + " Cognition	
Coronary Artery Risk Development in Young Adults (CARDIA)	African American (45%)	Longitudinal, 8.0 years	*N* = 2621; 25 (3.5)	Mediterranean diet	Cognitive Scores assessed 25 and 30 years later	↑ Cognitive function in midlife (McEvoy et al., 2019)	Not reported
57% female				DASH diet		No association	

(Continued)

TABLE 1 | Continued

Cohort and study population	Minority population%	Years Follow-up	N; Mean Age (*SD*)	Exposure	Outcome	Findings	Exposure Interaction with Race
				A Priori Dietary Quality Index		↑ Cognitive function in midlife (McEvoy et al., 2019)	
REGARDS- REasons for Geographic And Racial Differences in Stroke	African American (31%)	Longitudinal 4–7 years	*N* = 18,080; 64.4 (9.1)	Plant-based diet Southern diet	Incident cognitive Impairment	↓ Incident cognitive impairment (Pearson et al., 2016) ↑ Incident cognitive impairment (Pearson et al., 2016)	Diet*race not significant *No stratified analysis by race*
				Mediterranean diet		↓ Incident cognitive Impairment in non-diabetic participants (Tsivgoulis et al., 2013)	Only Diet*diabetes significant. Stratified by diabetes status
HANDLS (Healthy Aging in the Neighborhood of Diversity Across Lifespan) Participants (Biracial) 57% female	African American (51%)	Cross-sectional	*N* = 2090; 47.9 (9.2)	HEI-2010	Cognitive Scores	" + " Cognition only in those below the poverty line (Beydoun et al., 2018a)	Diet*race not significant *No stratified analysis by race*
				Dietary Antioxidant vitamins		Vitamin E " + " Cognition (Beydoun et al., 2015)	Vitamin E*race not significant *No stratified analysis by race*
		Longitudinal, 4–5 years		Dietary Vitamin D	Cognitive decline	↓ Cognitive decline (visual memory) (Beydoun et al., 2018b)	Vitamin D* race interaction significant: Improved visual memory only in Whites and not in Blacks
				Nutrient adequacy score (NAS) Caffeine Alcohol		" + " Cognition ↓ Attention decline (Beydoun et al., 2014) " + " Cognition " + " Attention and Working memory (Beydoun et al., 2014)	NAS*race not significant *No stratified analysis by race*
Two Boston based cohorts (Boston Puerto Rican Health Study (BPRHS) and Nutrition, Aging and Memory in Elders (NAME) study)	African American (37%) BPRHS- Hispanics (100%)	Cross-sectional	*N* = 1956,	Plasma Vitamin B12 Vitamin B6 Folate Homocysteine	Cognitive Scores	" + " Cognition (Moorthy et al., 2012) " + " Cognition No association No association	Not reported *No stratified analysis by race*
BPRHS (Boston Puerto Rican Health Study), 70% female	Hispanics (100%)	Cross-sectional	N = 1269, 57.3 (7.6)	Mediterranean diet HEI-2005	Cognitive Impairment	"–"cognitive impairment (Ye et al., 2013b)	N/A
				Fruits and Vegetables		"–" Cognitive Impairment (Ye et al., 2013a)	
		Longitudinal 2 years		Dietary n-3 and n-6 PUFA	Cognitive decline	EPA, DHA and n3VLCFA ↑ Executive Function (Bigornia et al., 2018)	
				Plasma vitamin B-6		↓ Cognitive decline (Palacios et al., 2019a)	
				Serum vitamin D		No association (Palacios et al., 2019b)	

*↑ Upward arrow indicates statistically significant increased risk in longitudinal analysis; ↓ downward arrow indicates statistically significant decreased risk in longitudinal analysis; " + " Plus indicates statistically significant positive association in the cross-sectional analysis; "–" Minus indicates statistically significant negative association in the cross-sectional analysis. *Dietary pattern for study population identified based on Reduced Rank Regression.*

Willett and Block FFQs have been well-validated by biochemical measures and other assessment methods of dietary intake, but their development and validation have been primarily in majority white populations. Thus, implementation of these tools in study populations that include other racial and ethnic groups without validating them raises concerns as to the validity of the study findings. It is possible that the absence of racial/ethnic differences in the diet-dementia findings in **Table 1** is due in part to the lower validity of the diet assessment tools to capture intake in the minority groups in some cohorts. Only a few of the cohort studies conducted validation studies of the FFQ within their study populations. Of these few, the validation correlations were somewhat moderate for Chicago Health and Aging Project participants (average $r = 0.41$ in African American vs. $r = 0.51$ in whites for 15 nutrients), and the WHICAP studies ($r = 0.40$ for 7 nutrients, correlations not reported by race/ethnicity). To validly assess diet, the FFQ should capture the most commonly consumed food items for a group as well as culture-specific recipes, cooking methods, and portion sizes. For example, Hispanics consume a bigger rice portion in one meal compared to whites and African American (Tucker et al., 1998). The standard portion size for rice among Puerto Ricans may be 1 cup versus 1/2 cup in non-Hispanic whites (Tucker et al., 1998). Food preparations, preference, cooking methods and recipes of dishes may vary too. For example, one study documented that soul food, a common dietary pattern found in African American culture, contains mainly pork, pork fat, chicken, organ meats, corn, sweet potatoes, and greens (Sucher and Kittler, 2004). The diets of different race/ethnicities in a study population will be well measured only to the extent that the appropriate foods, portions and preparation methods are accurately captured by the assessment method; for example, the Boston Puerto Rican Health Study uses a validated FFQ specifically designed and processed as per the Puerto Rican dietary habits. Similarly, the Jackson Heart Study used a validated FFQ developed based on regional food patterns rather than on the national patterns for whites and African Americans in the lower Mississippi Delta region (Tucker et al., 2007). Thus capturing diet using a validated tool for multi-ethnic populations is an important gap that can be improved in the field of diet and dementia.

The majority of studies on nutrition and dementia outcomes primarily based their findings on dietary intake levels of nutrients and foods. However, our knowledge about nutritional effects on the brain would be greatly enhanced by the addition of biochemical measures. There may be differences in nutrient absorption, metabolism, or delivery to tissues that require different intake levels by race/ethnicity for optimum brain function and disease prevention. The use of biochemical measures in conjunction with dietary intake assessments could be used to better inform public policy on recommended dietary intake levels by race. The reporting of dementia outcomes by level of nutrient intake as well as biochemical level is crucial to advance the field as well as to establish public health and clinical recommendations. Published studies rarely present this information stratified by race or ethnic group; even fewer report biochemical assessments.

Currently, there is much attention on the Mediterranean diet for dementia prevention. However, the promotion of one diet pattern for diverse cultures around the world may not be optimal from the perspective of public health or the environment. It is becoming evident that there are multiple diet patterns favorable to brain health. Given the challenges in achieving behavior change over the long-term, it does not appear feasible to expect individuals to adopt a single diet from a foreign culture that involves introducing new foods that are strange to one's usual cultural practices, or the elimination of favorite meal items. This approach to behavior change has a high likelihood of failure, particularly if the changes are more expensive. A "one diet" approach to health also would not prove favorable for environmental health. The ecological or carbon footprint may be unnecessarily large due to shipping and storage, particularly if there are local foods and diets that are equally beneficial for maintaining brain health. By studying nutrition and brain health in different cultures, regions, and races, we can identify multiple brain-healthy diets within a region and group. This is another large gap in the field.

FUTURE RESEARCH

In order to advance the field on nutrition and dementia in minority populations, it is imperative that the few studies with large minority populations report estimates of effect stratified by racial/ethnic group, at the very least in supplemental tables. In addition, new multi-racial/ethnic cohort studies are needed that include culturally appropriate and validated diet assessments as well as biochemical measures of nutrient status. Currently, there is limited data on a number of large minority populations in the U.S., particularly those originating from Mexico and other Latin American countries, Asia, and Native Americans. The inclusion of diverse cultures in a study lends to a greater range of nutrient intake levels and thus improved ability to observe diet-dementia relations. The diversity in dietary practices may also lead to discoveries of new nutrients and foods that are important in the disease process. Additionally, we need to understand how cognition is related to the nutrigenomics and nutrigenetics, i.e., two-level interaction between nutrients and genomics. Firstly, nutrients may affect transcriptional factors and modify the gene expression. Secondly, the genetic variability may define the interaction between nutrients and the disease (Fenech et al., 2011; Peña-Romero et al., 2018). Precision nutrition is gaining popularity for other disease outcomes, and future studies in the field of nutrition and cognition focusing on the genetic factors that may alter the relation of various foods with the brain health are needed. The emerging science on the gut microbiome and the gut-brain axis is a new frontier in the dementia field that would be greatly enhanced by diversity in diet that comes with the inclusion of multiple cultures within a study. Another frontier is the measurement of nutrients and metabolites in human brain tissue (Morris et al., 2003, 2015a) and their relations to measures of brain neuropathology. To date, these rare studies have largely been restricted to non-Hispanic whites. Finally, the first diet intervention trials on cognitive health have been initiated. Efforts to test diet approaches in multiple racial/ethnic groups is imperative for better understanding of the disease

process and for more effective public health policies to reduce racial/ethnic disparities in dementia.

AUTHOR CONTRIBUTIONS

PA: manuscript preparation and critical review. MM and LB: manuscript preparation and critical review of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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