

Beta-amyloid and Cortical Thickness Reveal Racial Disparities in Preclinical Alzheimer's Disease



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ABSTRACT

African Americans are two to four times more likely to develop dementia as Non-Hispanic Whites. This increased risk among African Americans represents a critical health disparity that affects nearly 43 million Americans. The present study tested the hypothesis that older African Americans with elevated beta-amyloid would show greater neurodegeneration (smaller hippocampal volumes and decreased cortical thickness) than older Non-Hispanic Whites with elevated beta-amyloid. Data from the Harvard Aging Brain Study (HABS) were used to form a group of older African Americans and two matched groups of Non-Hispanic White adults. Amyloid-positive African Americans had decreased cortical thickness in most of the Alzheimer's disease (AD) signature regions compared with amyloid-positive Non-Hispanic Whites. This factor was negatively correlated with age and white matter hypointensities. Using support vector regression, we also found some evidence that African Americans have an older "brain age" than Non-Hispanic Whites. These findings suggest that African Americans might be more susceptible to factors causing neurodegeneration, which then might accelerate the rate of a diagnosis of AD.

1. Introduction

As the age of the U.S. population rapidly increases, neurodegenerative diseases like Alzheimer's disease (AD) and other dementias also increase. Incidence rates of AD suggest that African Americans might be 2 to 4 times more likely to be diagnosed with AD than Non-Hispanic Whites (Heyman et al., 1991; Perkins et al., 1997; Steenland et al., 2016; Tang et al., 2001).¹ This increased risk among African Americans represents a critical health disparity that affects nearly 43 million Americans. Unfortunately, the causes of this disparity are not well understood. The greater incidence estimates have been attributed to measurement bias or referral bias (Shadlen et al., 1999), socioeconomic factors such as low education (Bennett et al., 2003; Callahan et al., 1996; Stern et al., 1994), and potential additive effects of comorbid conditions such as cerebrovascular disease (Manly et al., 1999; Sandberg et al., 2001). More recently, research has focused on socio-cultural factors that increase stress among African Americans (Cohen and Janicki-Deverts, 2012). Stressors from recent models focus on psychological stress resulting from factors such as discrimination and residential segregation and physical stress resulting from factors such as poor access to quality healthcare and greater exposure to environmental toxins (Chiao and Blizinsky, 2013; Hill et al., 2015). The present

study proposes that all of these factors compound to create a neurobiological vulnerability among African Americans. This vulnerability could take the form of greater accumulation of AD-related pathology (e.g., beta-amyloid; A β) and/or greater neurodegeneration (e.g., smaller volumes or cortical thickness).

The *Weathering Hypothesis* proposed by Geronimus (1992) provides the most relevant framework for interpreting race-related differences in biological processes. According to this hypothesis, the cumulative impact of the aforementioned social, physical, and economic adversities faced by African Americans lead to early health deterioration and advanced biological aging. For example, Geronimus et al. (2006) used data from the National Health and Nutrition Examination Survey (NHANES IV) to investigate whether young and middle-aged African Americans had a greater biological stress score as measured through 10 biomarkers (including blood pressure, body mass index, C-reactive protein, total cholesterol, among others) compared with Non-Hispanic Whites. They found that the mean biological stress score among African Americans was similar to that for Non-Hispanic Whites who were 10 years older, suggesting that stressors among African Americans led to accelerated aging (see also, Levine and Crimmins, 2014; Thorpe et al., 2016). Thus, this hypothesis suggests that African Americans might have poorer cardiovascular, metabolic, and immune health.

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¹ Hispanic Whites also show racial disparities in the diagnosis of AD (e.g., Perkins et al., 1997; Tang et al., 2001). The present study focused on African Americans due to the greater disparity in African Americans relative to Hispanic Whites.

Although not the focus of the Weathering Hypothesis, these general ideas might also extend to brain health. Research has suggested that prolonged exposure to such adversities can have negative impacts on the brain, including direct structural damage to neurons and initiates a series of secondary signals involving inflammation and oxidative structural damage (both of which are evidenced in AD; Nogueira et al., 2016). Furthermore, such adversities might reduce the brain's ability to resist subtle brain damage and increase the brain's vulnerability to pathological toxins including AD-related pathology (Gilbertson et al., 2002; Sapolsky et al., 1986). These toxins build over time and eventually lead to cell death that causes memory and attention problems often found in early stages of AD (Albert et al., 2011; Albert et al., 2001; Hamel et al., 2015). In fact, biological markers like telomere length that represent cumulative exposure to oxidative stress differs by race (Diez Roux et al., 2009). Thus, the AD process might be accelerated among African Americans, thus leading to a higher rate of AD.

These ideas have two implications for the development of AD among African Americans. One possibility is that African Americans might build up AD-related pathology at a faster rate compared with their White counterparts. However, assessments of AD-related pathology in postmortem samples have not found differences between African Americans and Non-Hispanic Whites (Riudavets et al., 2006; Sandberg et al., 2001). In fact, Sandberg et al. (2001) found that A β was consistently lower among African Americans than in Non-Hispanic Whites. Conflicting with these postmortem findings, a recent study using PET imaging in cognitively-normal older adults found that in vivo estimates of A β using Florbetapir was higher among African Americans than Non-Hispanic Whites (Gottesman et al., 2016). These results were maintained even after controlling for cardiovascular differences, but were no longer significant when excluding people with mild cognitive impairment (MCI).

A second implication of the Weathering Hypothesis is that instead of having higher levels of AD pathology, African Americans might have different rates of neurodegeneration than Non-Hispanic Whites (Sandberg et al., 2001). Consistent with this idea, cognitively-normal African Americans who had high levels of A β deposition had greater 20-year cognitive declines than Non-Hispanic Whites who also had high levels of A β deposition (Gu et al., 2015). While this study supports the idea that early AD pathology might impact African Americans more than Non-Hispanic Whites, it was not clear whether the study controlled for initial levels of cognition or whether African Americans also had higher levels of A β than Non-Hispanic Whites. Thus, more research is necessary to understand the relationship between A β deposition and neurodegeneration in African Americans and Whites.

The present study tested the Weathering Hypothesis in the context of brain health in cognitively-normal African American and White older adults. Cross-sectional data were used from the Harvard Aging Brain Study (HABS) that includes MRI, PET imaging, and cognitive measures (Dagley et al., 2015). To the extent that African Americans respond to the accumulation of A β differently than Non-Hispanic Whites, it was predicted that African Americans with high A β deposition would show greater neurodegeneration than Non-Hispanic Whites with high A β deposition. Neurodegeneration was measured using a ratio between the hippocampal and ventricle size (Heister et al., 2011), as well as cortical thickness in a set of nine brain regions previously shown to decline in AD (Bakkour et al., 2009; Dickerson et al., 2008). No predictions were made regarding which specific brain regions would show the greatest associations. We also tested the extent that any race-related differences in brain structure might be more pronounced by various factors known to convey advanced risk of AD including older age, fewer years of education, lower verbal IQ, and existing white matter damage. Lastly, we tested another prediction made by the Weathering Hypothesis: African Americans would have a greater biological age than Non-Hispanic Whites.

2. Materials and methods

2.1. Participants

Data used in the preparation of this article were obtained from the HABS study (P01AG036694; <http://nmr.mgh.harvard.edu/lab/harvardagingbrain>). HABS was launched in 2010 and is led by principal investigators Reisa A. Sperling, MD and Keith A. Johnson, MD at Massachusetts General Hospital/Harvard Medical School in Boston, MA. Details of the study including recruitment criteria and all the measures conducted can be found in Dagley et al. (2015). Participants underwent MRI scanning, PIB-PET scanning, neuropsychological testing, and clinical assessments. The current data consists of version 1.0 and was downloaded in September 2016 and consisted of demographic information, behavioral measures, T1 summary scores, and A β summary scores. No other data were publicly available. The University of Alabama IRB has approved the use of this data.

Out of 284 older adults (aged 62–90) in the full sample, 43 of the participants reported being African American and 232 reported being White (see Table 1). To investigate racial differences, African Americans were divided into groups of high and low A β using a DVR score of 1.18 that achieved similar group sizes (21 high A β and 22 low A β) and is similar to previously used cut-offs in the HABS data set (e.g., Mormino et al., 2014). The high and low A β groups of African Americans were matched to the same number of high and low A β Non-Hispanic Whites (see Statistical analysis section). In addition to this matched group of non-Hispanic Whites, a second group of non-Hispanic Whites was formed to generalize the results to another sample. This second group was not matched as closely, which also allowed for more natural variations between races to emerge (e.g., cognitive performance).

2.2. MRI acquisition and analysis

MRI scanning was completed at the MGH Martinos Center using a Siemens TIM Trio 3 T System with a 12-channel head coil. Structural T1-weighted volumetric magnetization-prepared, rapid acquisition gradient echo (MPRAGE) scans were collected with one of two acquisitions: ADNI1 MPRAGE (TR/TE/TI = 2300/2.98/900 ms, flip angle = 9°, 1 × 1 × 1.2 mm resolution, 0 acceleration) or ADNI2GO MPRAGE (TR/TE/TI = 2300/2.95/900 ms, flip angle = 9°, 1.1 × 1.1 × 1.2 mm resolution, 2 × GRAPPA acceleration). These two acquisitions are considered interchangeable.

Region of interest (ROI) labeling was implemented using FreeSurfer v5.1. Cortical ROIs were defined using the Desikan-Killiany atlas. Subcortical ROIs were defined using the Freesurfer aseg atlas. Freesurfer preprocessing quality was manually assessed by examining the white and pial surface segmentation. In cases where dura or skull influenced the segmentation result, voxels were either manually edited or corrected by adjusting the watershed threshold. Control points were added to the image and/or white matter edits were made when the grey matter ribbon clearly included white matter or excluded grey matter.

Indices of neurodegeneration consisted of an estimate of hippocampal decline (hippocampal occupancy (Heister et al., 2011)) and cortical thickness in AD signature regions (Bakkour et al., 2009). Left and right hippocampal volumes and the inferior lateral ventricles were corrected using intracranial volume estimates. Then, hippocampal occupancy scores were created by dividing hippocampal volume by the sum of the hippocampal volume and the inferior lateral ventricle volume for each hemisphere, separately. The hippocampal occupancy score has advantages over simple measures of hippocampal volume because cross-sectional measures of hippocampus volume confounds baseline levels (i.e., individual difference) with longitudinal decline (Heister et al., 2011). By considering the size of the inferior lateral ventricle, estimates of longitudinal atrophy that control for baseline levels of volume size can be obtained. Cortical thickness was extracted

Table 1
Demographic characteristics.

	African American A β -low	African American A β -high	White A β -Low (matched)	White A β -High (matched)	White A β -Low (unmatched)	White A β -High (unmatched)	χ^2 (df) or F (df _b , df _w) (matched)	χ^2 (df) or F (df _b , df _w) (unmatched)
N	22	21	22	21	22	21		
Age (years)	72.41 (7.91)	72.77 (4.65)	72.53 (6.21)	74.11 (6.54)	73.60 (6.47)	73.68 (6.57)	0.31 (3, 82)	0.20 (3, 82)
Age range	62–88	65–83	65–89	65–90	66–86	64–85		
Sex (M/F)	5/17	6/15	7/15	6/15	5/17	9/12	0.00 (1)	0.03 (1)
Education (years) ^{a,b}	13.45 (2.61)	15.24 (2.55)	13.046 (3.42)	16.10 (2.57)	14.82 (2.81)	14.43 (2.66)	5.68 (3, 82)	1.78 (3, 82)
Education range	9–18	12–20	6–20	12–20	8–18	11–18		
MMSE score ^c	28.50 (1.57)	28.29 (1.35)	28.82 (1.18)	28.57 (1.17)	29.32 (0.95)	29.33 (0.80)	0.59 (3, 82)	4.38 (3, 82)
MMSE range	26–30	25–30	26–30	27–30	27–30	28–30		
GDS score	3.18 (3.03)	2.62 (3.09)	2.55 (2.96)	2.76 (2.77)	3.05 (2.72)	3.76 (3.24)	0.20 (3, 82)	0.51 (3, 82)
GDS range	0–10	0–9	0–11	0–11	0–9	0–12		
AMNART score ^c	112.77 (8.55)	110.52 (13.77)	112.86 (7.49)	115.38 (9.78)	121.59 (6.01)	122.86 (4.83)	0.81 (3, 82)	10.25 (3, 82)
AMNART range	95–129	78–129	99–123	96–128	108–130	114–129		
Mean precuneus A β ^{a,b}	1.11 (0.04)	1.35 (0.20)	1.11 (0.05)	1.36 (0.20)	1.12 (0.04)	1.31 (0.15)	20.64 (3, 82)	21.23 (3, 82)
Range precuneus A β	1.01–1.17	1.19–1.78	0.99–1.17	1.18–1.74	1.01–1.18	1.18–1.75		
Mean WM hypointensity volume (mm ³)	4783.96 (3077.98)	6526.48 (5325.60)	4520.18 (3578.32)	7842.10 (11,782.69)	3976.41 (4015.35)	5252.67 (7359.56)	1.12 (3, 82)	0.91 (3, 82)
Range WM hypointensity volume (mm ³)	1517–11,499	2164–24,237	1866–15,242	1988–55,409	1413–20,245	1763–35,983		

Notes. A β = Beta-amyloid; MMSE = Mini-Mental State Exam; GDS = Geriatric Depression Scale; AMNART = American National Adult Reading Test; WM = White Matter; Standard deviations in parentheses.

^a Significant main effect of A β Status (A β -High > A β -Low) in matched group.

^b Significant main effect of A β Status (A β -High > A β -Low) in unmatched group.

^c Significant main effect of Race (White > Black) in unmatched group.

from nine ROIs from each hemisphere that most closely corresponded to the AD signature regions: entorhinal cortex, inferior temporal gyrus, temporal pole, inferior parietal cortex, superior parietal lobe, supra-marginal gyrus, precuneus, superior frontal gyrus, and parsopercularis.²

Estimates of white matter damage were assessed using volumes of white matter hypointensities from the T1-weighted structural scan using Freesurfer. White matter hypointensities serve as markers for axonal damage and demyelination (Garel et al., 2004; van Walderveen et al., 1998). Note that the more commonly used assessment of white matter damage (from T2 scans) was not released for public analysis. Nevertheless, correspondences have been found between white matter lesions on T1 and T2 scans (Bakshi et al., 2001). Furthermore, T1 hypointensities can have greater pathologic specificity than T2 hyperintensities for severe demyelination and irreversible tissue loss (van Walderveen et al., 1998).

2.3. PET image acquisition and analysis

C11-PIB imaging was performed using a Siemens ECAT EXACT HR + PET scanner. Before injection, 10-min transmission scans for attenuation correction were collected. After injection of 8.5–15 mCi PIB, 60-min of dynamic data were acquired in 3D acquisition mode. Data were manually evaluated and corrected for motion. Then, a mean image was created by averaging across the first 8 min of data acquisition and used for co-registration.

The present study used Freesurfer ROIs from the Desikan-Killiany atlas to extract mean DVR values from the mean PET image. Each PET image was coregistered to that subjects T1 Freesurfer processed structural image and mapped into native PET space. The native space labels were then used to make ROI measurements computed using the Logan plot method with cerebellar grey matter as the reference region. The present study averaged left and right precuneus ROIs an indicator of A β deposition, which is one of the earliest regions to accumulate A β in AD

² Because neither the raw anatomical nor processed Freesurfer files were released, more focused ROIs to match the original AD Signature Regions could not be used (e.g., Bakkour et al., 2009; Dickerson et al., 2008; McDonough et al., 2016).

(Jagust, 2009), shows some of the greatest cortical PIB binding (Mintun et al., 2006; Rowe et al., 2007), has some of the highest inter-rater reliability scores (Rosario et al., 2011), and shows the strongest difference between normal controls and AD patients (Rowe et al., 2008).

2.4. Statistical analysis

Propensity score matching (e.g., d'Agostino, 1998; Dehejia and Wahba, 2002) was used to create four groups of participants (A β -High African Americans, A β -High Non-Hispanic Whites, A β -Low African Americans, and A β -Low Non-Hispanic Whites). This procedure reduces confounds between the comparison groups of interest and is especially suitable for matching uneven sample sizes (e.g., Brookhart et al., 2013). First, the entire sample of participants was divided into low and high A β groups using a DVR cut-off of 1.18 (similar to Mormino et al., 2014), regardless of race and ensured equal cut-offs for both groups. Note that preliminary analyses indicated that African Americans did not differ in mean level A β than Non-Hispanic Whites ($M = 1.23$, $SD = 0.18$ and $M = 1.23$, $SD = 0.20$, respectively).

Separately for the high A β and low A β groups, propensity scores were implemented using the MatchIt package (Ho et al., 2011) in R (Team, 2014). A logistic regression was first estimated using race as the dependent variable and the matching factors of interest as the independent variables that included age, sex, years of education, MMSE score, verbal IQ, A β level, and white matter hypointensities. The propensity score for each individual was calculated using the person's predicted probability of being African American, given the estimates from the logistic regression model. Then, pairs of observations that had similar propensity scores, but differed in race, were matched using the nearest neighbor method, which matched the closest control for each treated unit one at a time (Gu and Rosenbaum, 1993). The result was a matched group of high A β Non-Hispanic Whites to the group of high A β African Americans and the same for the low A β groups. A 2 (Race: African American, White) \times 2 (A β Status: High, Low) analysis of variance (ANOVA) was conducted for demographic and brain factors (see Results for Sample characteristics). This process was then repeated to create a second (non-overlapping) group of non-Hispanic White

individuals whose characteristics could vary more freely, thus representing natural demographic differences between the two races from the sample (the “unmatched group”). Specifically, this second group was matched only on age, sex, and A β level.

To determine how brain structure differed with race and A β status, a multivariate technique called Barycentric Discriminant Analysis (BADA) was used (Abdi and Williams, 2010). BADA is a useful statistical technique to identify subtle group differences across many variables. For example, BADA has been used to differentiate patterns of brain activity among A β -High older adults, A β -Low older adults, and young adults (Rieck et al., 2015). BADA uses a between-class Principal Components Analysis to identify orthogonal factors of the inputted variables (e.g., brain regions) that finds orthogonal patterns that optimally differentiate between the specified groups. Specifically, a matrix of 20 brain structure ROIs and a dummy matrix representing the four groups were subjected to the generalized singular value decomposition. The factors resulting from this analysis represent how brain structure differs between the four groups. Bootstrapping procedures were used with 10,000 iterations to compute 95% confidence intervals. Bootstrap ratios above the critical value of 2 were considered significant at the $p < 0.05$ level. These analyses were implemented using the ExPosition and TInPosition packages (Beaton et al., 2014; Beaton et al., 2013) in R. In follow-up analyses, the relationships between brain structure and AD risk factors were assessed. Pearson correlations were conducted between the resulting factor scores and 1) age, 2) years of education, 3) verbal IQ, and, 4) white matter hypointensities.

To determine whether African Americans were biologically older than Non-Hispanic Whites, we entered the brain structure data into a support vector regression (SVR) to predict chronological age. SVR has been used in neuroimaging studies to build a model of age with a training set and predict the age of new instances using only neuroimaging data (e.g., Dosenbach et al., 2010) (see also Table 3). Thus, SVR can create a model of biological aging from which we can estimate the “brain age” of both African Americans and Non-Hispanic Whites. Using the e1071 package (Meyer et al., 2015) in R, an SVR model was made for each pair of groups (matched and unmatched) and with/without the inclusion of white matter hypointensities as a feature in the model to test the contribution of cardiovascular effects (four total models).

For each model, features included the brain regions exhibiting a significant effect in the above (BADA) analysis. Features were scaled and used to train a model to classify a participant's age using leave-one-out cross-validation. Using this validation technique, all participants were trained except for one to form the model. The model was then tested on the left-out participant, thus serving as a new and unbiased test with the result of a predicted age value for that participant. This procedure was repeated with a different participant left out and tested, resulting in each participant having an unbiased prediction of age (i.e., biological or brain age). Default parameters were used in each model (cost = 1, epsilon = 0.1). Root mean squared error (RMSE) was used to compare model fits with and without white matter hypointensities. To assess the similarity with predicted age and actual age, Pearson correlations were conducted for each model. To assess whether African Americans had a higher biological age than Non-Hispanic Whites, a 2 (Race: African American, White) \times 2 (A β Status: High, Low) ANOVA was conducted on the model-derived predicted age for each set of SVR models.

3. Results

3.1. Sample characteristics

For the matched samples, a 2 (Race: African American, White) \times 2 (A β Status: High, Low) ANOVA was conducted on the sample characteristics to identify any group differences (see Table 1). Significant main effects of A β Status were found for years of education (A β High > A β Low, $b = 1.78$, $t(82) = 2.08$, $p = 0.041$) and, by design,

level of A β (A β High > A β Low, $b = 0.24$, $t(82) = 5.52$, $p < 0.001$). No group differences or interactions were found in regard to age, MMSE, GDS, verbal IQ, or white matter hyperintensity volumes (all p 's > 0.27). Thus, African Americans and non-Hispanic Whites did not differ from each other on any measures of interest within the respective A β -High and A β -Low groups.

For the unmatched samples, the same ANOVA was conducted. A significant main effect of A β Status was found for years of education (A β High > A β Low, $b = 1.78$, $t(82) = 2.20$, $p = 0.031$) and, by design, a significant main effect of A β Status also was found (A β High > A β Low, $b = 0.24$, $t(82) = 6.25$, $p < 0.001$). Significant main effects of Race were found for MMSE score (Non-Hispanic Whites > African Americans, $b = 0.81$, $t(82) = 2.25$, $p = 0.027$) and verbal IQ (Non-Hispanic Whites > African Americans, $b = 8.82$, $t(82) = 3.27$, $p = 0.0016$). A marginal Race \times A β Status interaction was found for years of education ($b = 2.17$, $t(82) = 1.89$, $p = 0.062$), such that the A β -High African Americans had more education than A β -Low African Americans, but A β -High Non-Hispanic Whites had less education than A β -Low Non-Hispanic Whites in the unmatched sample. While the nature of this interaction is unclear, this difference provides a strong test of reliability of the analyses given large heterogeneity in the unmatched samples. No other effects were found.

3.2. Effects of race and A β status on brain structure

Because four groups were submitted to the analysis, three factors (n groups - 1) were obtained. For the analysis in the matched samples, the three factors explained 91.32% (Factor 1), 6.74% (Factor 2), and 1.94% (Factor 3) of the total covariance in the data. The omnibus test of the final multivariate factor structure was significant, $p = 0.0021$. Of the three factors, only the first factor was reliable, $p = 0.0013$. As can be seen in Fig. 1, this factor was driven by brain structure differences between A β -High African Americans and A β -High Non-Hispanic Whites. Inspection of the direction of the effects indicate that A β -High African Americans had lower brain structural values than A β -High Non-Hispanic Whites. The bootstrap ratios indicated that 12 of the 20 brain regions significantly differed between these two groups (see Table 2). These significant regions included cortical thickness for bilateral superior frontal gyri, temporal pole, inferior parietal cortex, superior parietal cortex, supramarginal gyri, left entorhinal cortex, and right inferior temporal cortex.³

The results were highly similar for the unmatched samples. The resulting factors explained 88.94% (Factor 1), 8.43% (Factor 2), and 2.63% (Factor 3) of the total covariance in the data. The omnibus test of the final multivariate factor structure was significant, $p = 0.0002$. Of the three factors, only the first factor was reliable, $p = 0.0001$. As can be seen in Fig. 1, this factor was driven by brain structure differences between A β -High African Americans and A β -High Non-Hispanic Whites. The bootstrap ratios indicated that 14 of the 20 brain regions significantly differed between these two groups (see Table 2). These significant regions were the same as in the matched-sample analysis, but also included cortical thickness in the right parsopercularis and right precuneus.

³ The matching resulted in an individual from the high amyloid White (matched) group having a very large white matter hypointensity volume (> 55,000 mm³). Given that such a high volume might suggest more severe cerebrovascular disease, we recalculated the BADA results removing this participant. The BADA results were nearly identical to the original analysis. The first factor from the BADA model was significant ($p = 0.002$) and explained 92.07% of the covariance in the data. This factor again only separated the high amyloid African American from the high amyloid White group. All the brain regions from the original analysis were significant with the addition of right entorhinal thickness that was only significant in this new analysis. Thus, this participant resulted in a more conservative estimate of our results.

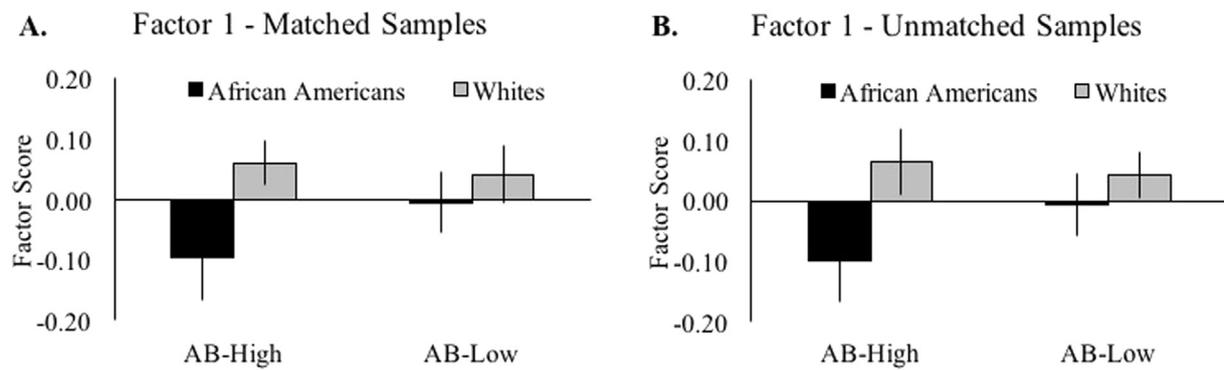


Fig. 1. Factor scores for the Barycentric Discriminant Analysis in the matched groups (Panel A) and in the unmatched groups (Panel B). The factor scores represent the weighted estimates of brain structure (hippocampal occupancy and cortical thickness) that varied between African Americans (black bars) and Non-Hispanic Whites (grey bars) who had high levels of beta-amyloid (Aβ; left) than those with low levels of Aβ (right). While the sign of the factor is arbitrarily chosen, inspection of the raw data indicates that Aβ-High African Americans had lower brain structural values than Aβ-High Non-Hispanic Whites.

Table 2
Bootstrap ratios for brain regions showing differences between Aβ-High African Americans and Aβ-High Non-Hispanic Whites.

Lobe	Region name	Bootstrap ratio (matched groups)		Bootstrap ratio (unmatched groups)	
		Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Frontal	Superior frontal Thk	2.48*	3.00*	3.11*	3.92*
	Parsopercularis Thk	1.90	1.78	1.54	2.22*
Temporal	Hippocampal Occupancy score	0.44	0.59	0.66	0.46
	Entorhinal Thk	2.92*	1.94	2.70*	1.79
	Inferior temporal Thk	1.05	2.43*	1.88	3.07*
	Temporal pole Thk	2.52*	3.72*	3.13*	3.38*
Parietal	Inferior parietal Thk	2.70*	3.54*	2.67*	3.87*
	Superior parietal Thk	2.69*	3.59*	2.75*	3.67*
	Supramarginal Thk	3.28*	4.09*	3.74*	4.67*
	Precuneus Thk	0.90	1.52	1.94	2.80*

Note.Thk = Thickness.
* $p < 0.05$.

Table 3
Predicted age derived from cortical thickness measures in the support vector regression analysis.

	Matched groups (without WMH)		Matched groups (with WMH)		Unmatched groups (without WMH)		Unmatched groups (with WMH)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
African Americans								
Aβ-Low	72.26	3.87	72.24	3.88	73.18	4.34	73.53	4.83
Aβ-High	73.20	3.21	73.14	3.17	75.08	3.67	75.17	4.09
Non-Hispanic Whites								
Aβ-Low	71.21	3.23	71.27	3.46	70.46	2.57	70.42	3.51
Aβ-High	70.93	3.22	71.64	5.38	70.10	3.34	70.82	4.00

Notes. SD = standard deviation; WMH = white matter hypointensities.

3.3. Brain factor correlations

To assess the relationship between the brain structure and AD risk factors, Factor 1 scores were correlated with and 1) age, 2) years of education, 3) verbal IQ, and 4) white matter hypointensities. For the matched samples, Factor 1 was negatively correlated with white matter hypointensities ($r(84) = -0.22$, CI $[-0.42, -0.01]$, $p = 0.038$), and marginally negatively correlated with age ($r(84) = -0.19$, CI $[-0.39, 0.02]$, $p = 0.075$). For the unmatched samples, these correlations were even stronger. Factor 1 was negatively correlated with white matter hypointensities ($r(84) = -0.29$, CI $[-0.47, -0.08]$, $p = 0.0078$), and negatively correlated with age ($r(84) = -0.41$, CI $[-0.58, -0.22]$, $p < 0.001$). Note that if Bonferroni corrections for multiple

comparisons were employed ($p = 0.0125$), only the correlations in the unmatched samples would be significant. Nevertheless, the similarity across the samples suggest that greater thickness in the significant AD signature regions associated with Factor 1 was related to AD risk factors (age and vascular disease).

3.4. Brain age of African Americans and non-Hispanic Whites

To assess whether African Americans have an older biological age than Non-Hispanic Whites, SVR models were created using the 12 significant brain regions that showed race differences with those with high Aβ levels and that overlapped across the analyses with the matched and unmatched groups. The SVR model with the matched groups that did

not include white matter hypointensities had an RMSE of 7.065 and a mean difference from the actual age of -1.05 years, suggesting the mean biological age estimated participants as slightly younger than their mean actual age. The predicted age from the model, however, did not significantly correlate with actual age, $r(84) = 0.072$, $CI [-0.14, 0.28]$, $p = 0.51$. The 2 (Race) \times 2 (A β Level) ANOVA on predicted age revealed no significant effects (p 's > 0.30), suggesting that African Americans' biological age did not differ from Non-Hispanic Whites in this model and is inconsistent with the Weathering Hypothesis. Adding white matter hypointensities to the SVR resulted in a higher RMSE of 7.52, suggesting a worse model fit than the previous model. The mean difference in predicted and actual age was -0.88 , suggesting a slightly younger biological age as in the previous model. The predicted age did not correlate with actual age, $r(84) = 0.072$, $CI [-0.20, 0.22]$, $p = 0.51$. The Race \times A β Level ANOVA on predicted age revealed no significant effects (p 's > 0.42).

For the analyses with the unmatched samples, a different pattern of results was obtained. The SVR model with the unmatched groups that did not include white matter hypointensities had an RMSE of 6.86 and a mean difference from the actual age of -0.92 years. In contrast to the previous models, the correlation between predicted age and actual age nearly reached significance, $r(84) = 0.21$, $CI [-0.003, 0.40]$, $p = 0.054$. The Race \times A β Level ANOVA on predicted age ($F(3, 82) = 9.46$, $p < 0.001$) revealed a significant main effect of Race ($b = 2.72$, $t(82) = 2.55$, $p = 0.012$), such that African Americans had an older predicted age than Non-Hispanic Whites. A marginal main effect of A β Level also was found ($b = 1.90$, $t(82) = 1.76$, $p = 0.082$), such that High-A β individuals had an older predicted age than Low-A β individuals. No significant interaction was found ($p = 0.14$). To test whether confounding factors within the group differences such as MMSE and verbal IQ contributed to these group effects, an ANCOVA was conducted controlling for both MMSE and verbal IQ. In this new analysis ($F(5, 80) = 6.27$, $p < 0.001$), Race remained significant ($b = 2.44$, $t(80) = 2.14$, $p = 0.035$) and A β Level remained marginal ($b = 1.83$, $t(80) = 1.69$, $p = 0.095$). Adding white matter hypointensities to the SVR resulted in a lower RMSE of 6.54, suggesting a better model fit than the previous model. The mean difference in predicted and actual age was -0.64 , suggesting a slightly younger biological age as in the previous model. The predicted age significantly correlated with actual age $r(84) = 0.33$, $CI [0.12, 0.50]$, $p = 0.0022$. In the Race \times A β Level ANOVA ($F(3, 82) = 6.39$, $p < 0.001$), only the main effect of Race was significant ($b = 3.12$, $t(82) = 2.50$, $p = 0.014$), such that African Americans had an older predicted age than Non-Hispanic Whites.⁴ To test whether confounding factors within the group differences such as MMSE and verbal IQ contributed to these group effects, an ANCOVA was conducted controlling for both MMSE and verbal IQ ($F(5, 80) = 5.07$, $p < 0.001$). Race remained significant ($b = 2.59$, $t(80) = 1.98$, $p = 0.051$).

4. Discussion

The present study investigated racial health disparities in AD-related pathology (A β deposition) and neurodegeneration (hippocampal

⁴ It is possible that the difference between predicted and actual age rather than predicted age, per se, would better capture differences between the four groups. A "relative age" score was calculated by subtracting actual age from predicted age, which formed the dependent variable. Race and A β Level were entered as the independent variables. As in the previous analysis using the matched groups, no significant effects of Race or A β Level was found on this relative age score. For the unmatched groups without white matter hypointensities included in the model, a main effect of race was found ($b = -3.92$, $t(82) = -2.01$, $p = 0.048$), such that the model predicted African Americans to be 4.88 relative years older than non-Hispanic Whites. For the unmatched groups with white matter hypointensities in the model, a main effect of race also was found ($b = -4.31$, $t(82) = -2.31$, $p = 0.023$), such that the model predicted African Americans to be 4.77 relative years older than non-Hispanic Whites. These findings are consistent with those when using the predicted age as the dependent variable.

volume and cortical thickness) in cognitively-normal older adults. According to the Weathering Hypothesis, the cumulative impact of social, physical, and economic adversities faced by African Americans lead to early health deterioration and advanced biological aging (Geronimus, 1992). The present study extended this hypothesis to brain health in the context of the AD process.

While cognitively-normal older African Americans in the present sample did not have higher levels of A β deposition than Non-Hispanic Whites, African Americans with elevated A β deposition did exhibit greater neurodegeneration in many AD signature regions compared with Non-Hispanic Whites with elevated A β deposition. Therefore, African Americans might have more neurodegeneration than Non-Hispanic Whites. The largest race-related differences in cortical thickness were found in lateral parietal cortex. Lateral parietal cortex is one of the first regions to show hypometabolism in AD (Herholz, 1995; Minoshima et al., 1997) and shows elevated A β deposition in cognitively-normal adults (across all races) relative to other brain regions (Klunk et al., 2004; Mormino et al., 2012). We also found that cortical thickness in regions that differed with A β deposition and race also correlated with chronological age, which is a known factor of AD (Launer et al., 1999). Together, this pattern might indicate that African Americans are further along in the AD process than Non-Hispanic Whites.

The Weathering Hypothesis also postulates that the additional wear and tear on the body through the various adversities encountered by African Americans would lead to more cellular deterioration, and thus "biologically age" them faster than non-Hispanic Whites. Using SVR, cortical thickness in the regions that differed in race and A β level served as inputs to form biological aging estimates (akin to a "brain age"). When these models were implemented in the matched samples, the biological estimates of age did not differ between either racial groups or A β groups. In contrast, when these models were implemented in the unmatched samples, African Americans were deemed biologically older than Non-Hispanic Whites by about 4 years. These results were strongest when white matter hypointensities were added to the model. This latter finding provides support for the Weathering Hypothesis and suggests that white matter damage (possibly as a result of cardiovascular disease) exacerbates the biological aging process.

The discrepancy between the findings in the matched and unmatched samples could be the result of the confounding factors between the groups in the unmatched samples such as verbal IQ and MMSE score. It could be the case that individuals with lower verbal IQ have thinner cortices, leading to an older biological age. Higher IQ has been associated with larger brain structure in regions that overlap with the significant regions found in the present study (e.g., Choi et al., 2008; for a meta-analysis, see Basten et al., 2015). Thus, higher verbal IQ might serve as a type of brain reserve that protects people from AD pathology (Katzman, 1993; Mortimer et al., 1981). Alternatively, the discrepancy between matched and unmatched groups could be due to differences in MMSE score. Lower MMSE scores might be associated with lower cortical thickness and an older biological age. Indeed, many studies have found associations between MMSE score and cortical thickness across a variety of brain regions (e.g., Avants et al., 2010; Bakkour et al., 2009; Du et al., 2007; Lerch et al., 2005). While controlling for both verbal IQ and MMSE score numerically reduced the effects of race on the biological age predictions, they remained significant. Therefore, differences in verbal IQ and MMSE cannot entirely explain the race differences in biological age.

As mentioned above, certain factors that have often been used to explain the Weathering Hypothesis include social and economic adversities faced by African Americans. While these adversities clearly exist historically and today, those factors do not seem to explain the neurodegenerative effects found in the present sample. The only available measure of socioeconomic status was years of education. Years of education was not only equated among the groups, but also did not significantly correlate with the factor scores representing

neurodegeneration. Recent research has noted that the quality of education, rather than simply the number of years in school may be more critical in explaining racial health disparities (e.g., Crowe et al., 2012; Liu et al., 2015). For example, while some African Americans may have gone to school for a similar number of years than their non-Hispanic White counterparts, the school term length per year was on average 20–30 days shorter (Crowe et al., 2012; Liu et al., 2015). Research has suggested that estimates of literacy (e.g., through pronunciation tasks) might be used as a proxy for education quality (e.g., Yaffe et al., 2013). In the present study, verbal IQ was assessed using a pronunciation task (i.e., AMNART) and was equated between the two races in the matched samples, suggesting that education quality also was not a strong contributor to the effects. Similar to years of education, verbal IQ was not correlated with the factor score in either the matched or the unmatched samples, further providing no support for the effect of quality of education on neurodegeneration.

One driving mechanism that might contribute to the greater neurodegeneration in high A β African Americans could be psychosocial stressors uniquely encountered by many African Americans including racial discrimination, residential segregation, and other social biases (Chiao and Blizinsky, 2013; Hill et al., 2015). Stress causes direct structural damage to neurons and initiates inflammation and oxidative structural damage, both of which are evidenced in AD (e.g., Nogueira et al., 2016). In addition to direct pathways of stress on potential structural neurodegeneration, stress has been shown to increase the amount of A β plaques in mice models of AD (e.g., Dong et al., 2004). Furthermore, in mice already with high A β , adding chronic stressors intensified the negative effects of A β on memory performance (e.g., Srivareerat et al., 2009). Thus, stress has the potential to accelerate neurodegeneration both directly and indirectly. In addition to the added psychosocial stressors that African Americans face, some African Americans have been shown to use maladaptive coping mechanisms such as keeping quiet and accepting poor treatment in the face of these stressors (e.g., Krieger, 1990). Psychosocial stress due to social disadvantages in African Americans has also been linked to increased alcohol problems (Mulia et al., 2008), which also are known to lead to neurodegeneration (e.g., Crews and Nixon, 2008; Wulff et al., 2010) and an earlier onset of AD (e.g., Harwood et al., 2010; Mukamal et al., 2003).

Factors other than social, physical, and economic adversities might also lead to enhanced brain vulnerabilities among African Americans. For example, African Americans often have higher rates of untreated hypertension and diabetes than Non-Hispanic Whites (Lloyd-Jones et al., 2010; Taylor et al., 2005). These cardiovascular disease risks might lead to greater rates of white matter lesions and cortical infarcts among African Americans compared with Non-Hispanic Whites. Studies have found that cardiovascular disease risks have a stronger relationship with the severity of white matter lesions among African Americans than Non-Hispanic Whites, suggesting that race can be a critical factor that moderates how external factors affect the brain (Liao et al., 1997). To account for white matter lesions, the present study included white matter hypointensities volumes taken from the T1 MRI scans. While these sources of white matter lesions did not differ between groups (in either the matched samples or the unmatched samples), individuals that had more white matter lesions consistently had less cortical thickness across all groups. However, including white matter lesions in the SVR models to estimate biological aging did not result in a greater biological age for African Americans than Non-Hispanic Whites. Overall, it appears that white matter lesions, at least as estimated by white matter hypointensities, is associated with more neurodegeneration, but is not race-specific.

While the present study is the first to show greater neurodegeneration among African Americans compared with Non-Hispanic Whites, more research is needed to replicate and generalize these findings. For example, geographical differences impact the level of social, physical, and economic adversities that African Americans experience. Older

African Americans living in the South historically experienced more widespread social inequalities than those in the North including experiencing the Jim Crow social structure, which resulted in lower levels of literacy and poorer health (Glymour and Manly, 2008). While yet to be seen, the findings from this study also may generalize to other populations that undergo a large degree of adversity including other minorities, people of low socioeconomic status, or people that work in extremely stressful environments.

One limitation of the present analysis was the small sample size of African Americans and Non-Hispanic Whites. While small for population studies of disease, most neuroimaging studies have about 20 participants per group as in the present study. Additionally, few neuroimaging studies include sufficient numbers of African Americans to investigate these critical health disparities, possibly because minorities are often less willing to participate in research (Corbie-Smith et al., 1999). Relatedly, the present sample of participants also might have been susceptible to selection bias. Older African Americans that were willing to participate in the study might differ from African Americans in the general population. The present study attempted to minimize these concerns by matching African American and White participants on numerous characteristics including age, sex, years of education, MMSE score, verbal IQ, A β level, and white matter hypointensities. In addition, African Americans were compared with a second group of White individuals with fewer matched characteristics to generalize the findings.

5. Conclusion

African Americans are estimated to have a greater chance of being diagnosed with AD compared with Non-Hispanic Whites, but the reasons for these health disparities are unclear. The present study provides a biological framework and initial tests of this framework to explain these disparities. African Americans that had high levels of A β were more likely to exhibit neurodegeneration compared to Non-Hispanic Whites that also had high levels of A β . The exaggerated declines in cortical thickness were also associated with older age and greater amounts of white matter lesions (independent of race), which might lead to an increased likelihood of being diagnosed with AD. Our working hypothesis is that race-related adversities are major contributing factors that make key brain regions more vulnerable to AD pathology and may contribute to advanced biological aging.

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