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Racial differences in gray matter integrity by diffusion tensor in black and white octogenarians

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Abstract

Objective—To quantify racial differences in brain structural characteristics in white and black octogenarians, and to examine whether these characteristics contribute to cognition.

Methods—Cross-sectional study of 283 adults 79–89 years old (59.4% white; 42.0% women) with data on gray matter integrity via diffusion tensor imaging (mean diffusivity), gray matter atrophy (GMA), white matter hyperintensities (WMH), literacy, smoking, drinking, income,

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Author Contributions:

Ge Liu: study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript. Ben Allen: analysis and interpretation of data, drafting the manuscript, and critical revision of the manuscript. Howard Aizenstein: acquisition of data, and critical revision of the manuscript. Robert Boudreau: analysis and interpretation of data, and critical revision of the manuscript. Anne Newman: acquisition of data, obtaining funding, and critical revision of the manuscript. Kristine Yaffe: critical revision of the manuscript. Stephen Kritchevsky: critical revision of the manuscript. Lenore Launer: critical revision of the manuscript. Suzanne Satterfield: critical revision of the manuscript. Eleanor Simonsick: critical revision of the manuscript. Caterina Rosano: study concept and design, acquisition of data, drafting the manuscript, critical revision of the manuscript, obtaining funding, and study supervision.

hypertension and diabetes. Participants were recruited from an ongoing epidemiological study of older adults living in the community with a range of chronic conditions, physical and cognitive function. Standardized betas (sβ) of neuroimaging markers predicting digit symbol substitution test (DSST) and modified mini-mental test (3MS) were computed in multivariable regression models stratified by race.

Results—Compared to whites, blacks had lower DSST (p=0.001) and lower 3MS (p=0.006), but also lower mean diffusivity (e.g. higher gray matter micro-structural integrity, p=0.032), independent of sex, income, literacy, body mass index, diabetes and drinking habits. Racial differences were not significant for WMH (p=0.062) or GMA (p=0.4). Among blacks, mean diffusivity and WMH were associated with DSST (sβ=−.209, p=0.037 and −.211, p=.038) independent of each other and of covariates; among whites, mean diffusivity, but not WMH, was significantly associated with DSST and 3MS (sβ =−.277, p=.002 and −.250, p=0.029).

Conclusions—In this cohort of octogenarians living in the community**,** blacks appeared to have higher microstructural integrity of gray matter as compared to whites. This neuroimaging marker was related to higher cognition even in the presence of WMH and other cardiovascular conditions. If confirmed, these findings suggest microstructural gray matter integrity may be a target to improve cognition, especially among blacks who survive to very old age with a range of chronic cardiovascular conditions.

Keywords

brain MRI; cognitive aging; DTI; racial differences

Introduction

Racial differences in dementia have been consistently reported and represent an urgent public health problem, but the underlying neural correlates of these differences are poorly understood. For example, several studies have found no significant racial differences in neuroimaging markers of overall brain integrity, including gray matter volume or white matter hyperintensities.[1–5] Two other studies reported that blacks are more likely to have severe white matter lesions, lower white matter integrity, and greater subclinical brain infarcts as compared to whites,[6, 7] but one study also reported lower brain atrophy in blacks compared to whites.[8]

Lower cardiometabolic health and socioeconomic status have been suggested as explanatory factors of racial disparities in cognition, but this evidence is also inconsistent. A recent longitudinal study of cognitively normal adults aged ≥ 65 years concluded that reducing ethnic disparities in diabetes could reduce racial differences in incident dementia by 17%.[9] Conversely, in another study of community-dwelling adults aged ≥ 70 years,[10] racial differences in cognition were not explained by stroke, hypertension, or diabetes.

Studies of racial disparities in cognition have seldom applied objective neuroimaging measures concurrent with assessment of cardiometabolic conditions. Moreover, many studies have relied on crude visual ratings of neuroimaging markers of macro-structural brain integrity, not accounting for micro-structural abnormalities in the brain’s parenchyma.

Diffusion tensor imaging of gray matter has been used to uncover micro-structural abnormalities, otherwise undetectable on conventional imaging. Higher mean diffusivity of gray matter may indicate loss of neurons, dendrites, and enlargement of extracellular space[26] in normal appearing gray matter. Specifically, mean diffusivity of gray matter is greater in relationship to older age,[27, 28] Alzheimer's Disease, and mild cognitive impairment.[29, 30]

In the current investigation, we integrate neuroimaging markers of micro- and macro-structure in elderly blacks and whites aged 79 to 89, whose cardiometabolic profile has been extensively characterized as part of the Health, Aging, and Body Composition study over the ten years preceding brain imaging. Specifically, we quantify the relative contribution of neuroimaging markers to performance on the mini-mental state examination test, which has been previously shown to be a marker of dementia in this cohort [11], and on the digit symbol substitution test, a well-established indicator of dementia, disability and mortality. [12–14]

Methods

Subjects

Participants of the Health, Aging and Body Composition study have been seen at regular intervals at the Pittsburgh site from 1997–98 to 2011–12. Participants were included irrespective of their cognitive status, e.g. formal dementia adjudication procedures were not hereby implemented. Of the 819 participants alive in 2006–07, 586 were invited to participate in a neuroimaging study of cognition and mobility, whereas the other 233 were not invited because they were walking with a cane and/or did not have mobility performance measures and/or they had been hospitalized for major clinic events in the previous 3 months (fracture, psychiatric problem). Among the 586 invited to the study, 99 were ineligible for a brain MRI, 145 were not interested or refused and 342 were eligible and interested. A total of 283 were included in this study because they had complete data on Diffusion Tensor Imaging (DTI) obtained via 3 Tesla magnet and DSST score. All participants signed a written informed consent and this study was approved by the institutional review boards of the University of Pittsburgh.

Demographic, Cardiometabolic Conditions, and Behavioral Risk Factors

Prevalent disease variables were computed at the time of MRI for coronary heart disease, hypertension, myocardial infarction, stroke and diabetes, using data collected since study entry in 1997–98, including self-reported information, physician diagnosis, medical history and Health Care Financing Administration data. Determination of cardiovascular disease included self-reported coronary heart disease, cerebrovascular disease or Health Care Financing Administration report of stroke. Study participants with average sitting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg concurrently or before the year of MRI were classified as hypertensive. Diabetes mellitus status was determined through self-report, use of hypoglycemia medication, a fasting glucose of ≥ 126 mg/dl, or a 2-hour glucose tolerance test ≥ 200mg/dl, in accordance with the American Diabetes Association criteria in 2002.

Age was calculated as number of years from date of birth to the MRI date. Body mass index was calculated as weight (kg)/height^2 (m) at time of MRI. Education and family income were collected in 1997–98, and were dichotomized at > high school education and at ≥ 25,000 dollars annually, respectively. Health literacy was quantified at time of MRI using the score from the Rapid Estimate of Adult Literacy in Medicine, and was dichotomized at literacy level ≥ 9th grade. Serum creatinine, smoking status, drinking status, and physical activities (kcal/kg/week, including walking and stairs climbing) were also measured at time of MRI.

Cognitive Assessment

The DSST was administered to all participants at regular intervals from study entry to time of MRI in 2006–07 according to a protocol previously described.[13] The DSST is a pencil-and-paper test of psychomotor performance[15], in which the subject is given a key-grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consists of filling in as many empty boxes as possible with a symbol matching each number. The testing time is 90 seconds. The score is the number of correct number--symbol matches. The strategy to solve the DSST consists of sequential encoding and retrieval of numbers and matching symbols. Short-term memory, perceptual organization, visuomotor coordination, and selective attention are important factors that determine performance. The DSST has high test-retest reliability.[16]

The modified mini-mental state examination (3MS) was administered to all participants at regular intervals from study entry to time of MRI. The 3MS is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory.[17] Possible scores range from 0 to 100, with higher scores indicating better cognitive function.

Image Acquisition

MRI scanning used a Siemens12-channel head coil and was performed on a 3T Siemens Tim Trio MR scanner at the MR Research Center of the University of Pittsburgh. Four series of MRI images were acquired on the MR scanner. Magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted images were acquired in the axial plane: TR=2300 ms; TE=3.43 ms; TI=900 ms; Flip angle=9°; slice thickness=1 mm; FOV=256 mm×224 mm; voxel size=1 mm×1 mm; matrix size=256×224; and number of slices=176. Fluid-attenuated inversion recovery (FLAIR) images were acquired in the axial plane: TR=9160 ms; TE=89 ms; TI=2500 ms; FA=150°; FOV=256mm×212 mm; slice thickness=3 mm; matrix size=256×240; number of slices=48 slices; and voxel size=1 mm×1 mm. DTI were acquired using single-short spin-echo echo planar imaging sequence with the following parameters: TR=5300 ms; TE=88 ms; TI=2500 ms; Flip angle=90°; FOV=256 mm×256 mm; two diffusion values of b =0 and 1000s/mm2; 12 diffusion directions; four repeats; 40slices; matrix size=128×128; voxel size=2 mm×2 mm; slice thickness=3 mm; and GRAPPA=2. A radiologist checked the MR images used in this study and excluded any unexpected findings from the study.

Image Processing and Analysis

Micro-structural integrity of the GM (mean diffusivity), WMH, GM and intracranial volumes were obtained using previously published methods, briefly described below.

The brain tissue volumes GM, WM, and cerebrospinal fluid (CSF), were calculated by segmenting the skull-stripped T1-weighted image in native anatomical space using the FAST–FMRIB's Automated Segmentation Tool (Zhang et al., 2001). The total GM volume, WM volume, and CSF volume were estimated in cubic millimeters by summing all voxels classified as these tissue types. Brain segmentation software usually includes the CSF between the surface of the brain and the interior of the skull, but does not always include all of the CSF between the inner skull and the brain. Total intracranial volume was computed as the volume contained within the "inner skull" using the brain extraction tool (BET) with an advanced option [18]. The WMH volume was obtained from T2-weighted FLAIR image using an automated method for quantification and localization of WMH [21]. The WMH quantification was done using a fuzzy connected algorithm [19, 20]. Total WMH volume was estimated by summing all the voxels classified as WMH. The total WMH volume was normalized for brain volume. Total GM volume was normalized by intracranial volume. Brain atrophy index was computed as: (ICV − total gray matter volume)/ICV.

DT MRI is a technique that uses the molecular diffusion of water within biologic tissue influenced by the characteristics of the surrounding medium [21]. Mean diffusivity (MD) is an average magnitude of molecular motion or measure of structural damage [22]). The diffusion-weighted images were pre-processed using the FMRIB's Diffusion Toolbox [23]) to remove unwanted distortions due to eddy current, the tensor were computed [24], and diagonalized to determine the eigenvalues from which the MD maps were computed [25].

Statistical Analysis

All sample characteristics were tested for racial differences using chi--square tests for dichotomous and t-tests for continuous variables. Due to the skewed distribution of 3MS, WMH, physical activity, and serum creatinine, medians and inter--quartile ranges were calculated, and median tests were used to test for racial differences. Analyses with 3MS were conducted with both raw 3MS and transformed 3MS (square root of (100-3MS)). Log transformed WMH was used in all analyses.

To test for racial differences in cognitive tests scores and in neuroimaging markers, linear regression models were constructed with race as the main independent variable, adjusted for variables that differed by race. The variation inflation factor was used to examine potential multicollinearity among model covariates. To appreciate the potential clinical relevance of the neuroimaging markers differing by race, multivariable linear regression models with DSST or 3MS as the dependent variable and the neuroimaging markers as the main independent variables were examined separately for blacks and whites, adjusted for other variables associated with DSST and 3MS.

In exploratory analyses to investigate selection bias, population characteristics of the participants with a clinic visit and a brain MRI in 2006–07 were compared to those of participants who returned for the clinic visit in 2006–07 but did not receive a brain MRI.

Survival bias analyses included all participants who entered the Health ABC study in 1997–98 at the Pittsburgh site, regardless of whether they returned for the clinic visit in 2006–07. Linear regression models were built with DSST or 3MS as dependent variable, and race, cohort (e.g. received a brain MRI), and the interaction of race by cohort as covariates. A significant interaction between race and cohort would be interpreted as an indication that racial differences in cognitive function among those included in this analysis were different from racial differences among those not included.

Results

Compared to whites, blacks consisted of more women, reported fewer years of education, lower health literacy and lower family income, but were of similar age (Table 1). Racial differences in cardiometabolic conditions indicated a higher cardiometabolic burden in blacks compared to whites; however, these differences were only significant ($p<0.05$) for diabetes and body mass index, not for other measures (Table 1).

In multivariable models adjusted for sex, literacy, drinking, income, diabetes, body mass index (e.g. those variables that differed by race), black race was associated with lower DSST and lower 3MS (Table 2) but also with lower MD, indicating higher gray matter integrity (Table 2). Racial differences in WMH were less strong and differences in GMA were not significant (Table 2).

Further study of the association between black race and lower mean diffusivity revealed that this association was robust to adjustment for those measures also known to be related to brain structural integrity (Table 3).

In race-stratified analyses of neuroimaging measures with cognitive tests (Table 4), higher mean diffusivity was associated with lower DSST in either race, independent of WMH and of other variables associated with DSST: literacy, income, current drinking and smoking (see Supplementary Table 1 for variables significantly associated with DSST). Mean diffusivity was inversely related with 3MS in either race, but associations were significant in whites and not in blacks. Adjustment for WMH, literacy, income and current drinking did not modify these associations (see Supplementary Table 1 for variables significantly associated with 3MS). Although WMH was also related to DSST and 3MS in blacks, it was not associated with DSST or 3MS in whites (Table 4).

Exploratory analyses to address selection bias showed that participants included in this study were more likely to be white, male, and have higher DSST and 3MS scores compared to the entire group of participants alive at time of the study (Supplementary Table 2). However, racial differences in DSST and 3MS in subjects included in this study were similar to those observed in the parent cohort at time of MRI (interaction terms of race by cohort for DSST and 3MS: $p=0.47$ and 0.84, respectively) Analyses to explore survival bias indicated that racial differences in DSST and 3MS detected at time of MRI in the subjects included in this analysis, were similar to and smaller than those observed in the parent cohort at study entry in 1997–98 (interaction terms of race by cohort for DSST and 3MS: $p=0.13$ and <0.01, respectively).

Discussion

In this study of very old adults living in the community, blacks who survived to a very old age had greater micro-structural gray matter integrity compared to whites of similar age; greater microstructural integrity was related to higher cognitive function independently of WMH. If confirmed, these results would suggest that gray matter microstructure could protect against cognitive impairment among older adults and this may be especially important for blacks displaying exceptional survival. Longitudinal studies are warranted to determine whether gray matter micro-structure buffers the negative impact of WMH on dementia risk.

While the determinants of gray matter micro-structural integrity are largely unknown, some evidence suggests that diabetes[31, 32] is related to lower gray matter microstructural integrity. Our analyses of the factors potentially contributing to mean diffusivity in this sample confirm these associations (Table 3). Further studies to identify factors related to mean diffusivity, and whether modification of these factors would yield changes in dementia risk via modification of mean diffusivity, are warranted. For example, initial studies show that the progression of structural brain abnormalities can be delayed by interventions on cardiometabolic risk factors late in life.[33–36] However, the effect of modification of these factors on microstructural integrity is not known.

Given the higher prevalence of cardiometabolic conditions in blacks compared to white, and the association of diabetes and hypertension with mean diffusivity in this sample, blacks of this cohort would be expected to have lower microstructural integrity. However, in our sample, the higher micro-structural integrity in blacks compared to white (e.g. lower mean diffusivity) was robust to adjustment to cardiometabolic conditions, including diabetes. Micro-structural abnormalities may accumulate over a long period time, whereas our measurements of cardiometabolic factors mostly extended to ten years prior to the neuroimaging measurements. It is possible that measurement of risk factors in mid-life would be more helpful to explain the racial differences in mean diffusivity hereby observed. Higher gray matter micro-structural integrity in blacks may also be a result of survival bias. The black participants of this sample appear to have survived to an exceptionally old age compared to 75 years of life expectancy at birth according to the national vital status reports 2010. Although we cannot completely rule out this possibility, racial differences in DSST were similar between participants of this study and those who were not alive at time of MRI. Furthermore, DSST values at time of MRI did not substantially differ from those excluded.

This study provides novel findings regarding racial differences in neuroimaging markers and the contribution to cognitive function. Our finding of racial disparities in DSST and 3MS is congruent with previous research.[1] Severity of cognitive impairment in our sample was also similar to that observed in the parent cohort.[37] However, the cross-sectional nature of this study limits our ability to determine whether longitudinal changes in gray matter integrity are paralleled by improved or stabilized cognitive performance. In addition, DSST and 3MS provide somewhat narrow indices of cognitive function. Since a complete cognitive adjudication was not available, we did not exclude participants based on their cognitive status and we cannot exclude that some of these participants may have had

underlying cognitive impairment already in place. Although this is a limitation of the study, it also warrants a higher heterogeneity of the sample. Future work should include a more comprehensive neuropsychological assessment with repeated neuroimaging measures and longer-term assessment of cardiometabolic factors.

Conclusions

If repeated, these findings support future work with very old adults of black and white ethnicity, to examine whether improving gray matter micro-structural integrity can offset the negative impact of WMH on cognitive function and possibly lower racial disparities in dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Racial differences in population characteristics. N (%) is reported unless noted otherwise.

Population characteristics	White (n =168)	Black (n =115)	p--Value[b]
Demographic factors			
Age (year), mean (SD)	83.2 (2.84)	82.7 (2.68)	0.20
Gender, female	84 (50)	79 (69)	0.001
Psychosocial factors			
Health literacy: ≥ 9th grade	150 (94)	72 (67)[d]	<.001
Education: >high school	101 (60)[d]	44 (38)	<.001[c]
Family income: ≥ 25K annual	99 (69)	36 (34)[d]	<.001[c]
Cardiometabolic conditions			
Diabetes[a]	35 (20)	41 (35)[d]	0.005[c]
Cardiovascular diseases[a]	47 (28)[d]	36 (31)	0.60[c]
Hypertension[a]	134 (80)	98 (86)	0.20
Coronary heart disease[a]	38 (22)[d]	29 (25)	0.60[c]
Myocardial infarction[a]	25 (15)[d]	20 (17)	0.60[c]
Stroke[a]	14 (8)	11 (9)	0.70
Body mass index (kg/m^2), mean (SD)	26.7 (4.02)[d]	28.6 (4.77)	<.001
Serum creatinine (mg/dL), median (IQR)	0.98 (0.84, 1.16)[d]	1.03 (0.87, 1.17)[d]	0.10[c]
Lifestyle and other factors			
Smoker, ever	77 (46)[d]	57 (50)[d]	0.60[c]
Drinker, current	106 (66)	34 (31)[d]	<.001[c]
Physical activity (kcal/kg/week), median (IQR)	2.7 (0.8, 7.4)	1.7 (0.4, 4.8)	0.10
ApoE, presence of allele 4	32 (29)	36 (23)[d]	0.20[c]

Abbreviations: IQR=inter--quartile range; SD=standard deviation

[a] Prevalence at time of MRI.

[b] p--Values were calculated from median test for physical activities and serum creatinine, from student's t--test for other continuous variables, and from Chi--squared test for categorical variables

[c] Statistically significant ($p<0.05$) differences between males and females in the whole sample.

[d] Statistically significant ($p<0.05$) differences between males and females within each race.

Table 2

Racial differences in brain structural measures and cognitive test scores.

	White (n =168)	Black (n =115)	P Value[c]
Brain structural measures:			
White matter hyperintensities [a], median (IQR)	0.0032 (0.0010, 0.0067)[e]	0.0041 (0.0011, 0.0124)	0.062
Gray matter atrophy [b], mean (SD)	0.72 (0.021)	0.72 (0.025)	0.4
Mean diffusivity, mm^2s^{-1}, mean (SD)	1.32 (0.106)	1.28 (0.114)	0.032
Cognitive tests:			
Digit symbol substitution test (DSST), points, mean (SD)	40 (12.56)	32 (13.49)	0.001
Modified mini--mental score (3MS), median (IQR), points	96 (93, 98)	91.5 (86, 96)	0.006

Abbreviations: IQR=inter--quartile range; SD=standard deviation

[a]White matter hyperintensities: total volume of white matter hyperintensities/total brain volume.

[b]Gray matter atrophy: (intracranial volume--gray matter volume)/intracranial volume.

[c]p--Values were calculated from linear regression models adjusted for sex, literacy, drinking, income, diabetes, body mass index.

Table 3

Racial differences in brain mean diffusivity in multivariable linear regression models. Dependent variable: mean diffusivity.

Model	Independent variable	Beta coefficient	Standard error	p--value
1	**Race, black**	−.041	.013	.002
2	**Race, black**	−.033	.013	.010
	Gender, female	−.041	.013	.002
3	**Race, black**	−.041	.014	.004
	Health literacy, ≥ 9th grade	.000	.019	.99
4	**Race, black**	−.045	.014	.001
	Education, >high school	−.019	.013	.16
5	**Race, black**	−.042	.014	.003
	Family income, ≥ 25K annual	−.005	.015	.72
6	**Race, black**	−.047	.013	.000
	Diabetes, present	.043	.015	.004
7	**Race, black**	−.038	.014	.006
	Body mass index, (kg/m^2)	−.002	.002	.28
8	**Race, black**	−.038	.014	.007
	Current drinker, yes	.007	.014	.62
9	**Race, black**	−.048	.014	.001
	Gender, female	−.047	.013	.001
	Education, >high school	−.027	.013	.04
	Diabetes, present	.037	.015	.01
	Hypertension, present	.028	.014	.04

Model 1: unadjusted.

Models 2 through 8: adjusted for variables that differed by race at $p<0.05$ (see Table 1); one variable entered each model.

Model 9: all the variables that differed by race at $p<0.05$ (see Table 1) entered this stepwise model, coefficients are reported for the variables retained in the last step.

Table 4

Race-stratified results of multivariable linear regression models of mean diffusivity and white matter hyperintensities predicting minimental substitution test and digit symbol substitution test scores.

Dependent variable	Independent variable	Standardized coefficient, p--value (Regression Coefficient (Standard Error))	
		Whites	Blacks
Digit symbol substitution	Mean diffusivity	−.277, p=.002 (−33.99 (10.79))	−.209, p=.037 (−23.09 (10.90))
	White matter hyperintensities	−.121, p=.2 (−3.00 (2.14))	−.211, p=.038 (−3.63 (1.73))
Minimental score	Mean diffusivity	−.250[1], p=.029 (−12.00 (3.97))	−.149[2], p=.080 (−9.93 (5.73))
	White matter hyperintensities	−.001[3], p=.8 (−.008 (.76))	−.253[4], p=.027 (−2.69 (.93))

[1] Standardized regression coefficients using square root transformed minimental score:.186.

[2] Standardized regression coefficients using square root transformed minimental score: .155.

[3] Standardized regression coefficients using square root transformed minimental score: .024

[4] Standardized regression coefficients using square root transformed minimental score: .198.

Models with DSST as outcome are adjusted for income, literacy, drinking, smoking;

Models with 3MS as outcome are adjusted for income, literacy, drinking.