Brain Morphology in Older African Americans, Caribbean Hispanics, and Whites From Northern Manhattan

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Background: Aging is accompanied by a decrease in brain volume and by an increase in cerebrovascular disease.

Objective: To examine the effects of age, sex, race/ethnicity, and vascular disease history on measures of brain morphology, including relative brain volume, ventricular volume, hippocampus and entorhinal cortex volumes, and white matter hyperintensity (WMH) burden, in a large community-based cohort of racially/ethnically diverse older adults without dementia.

Design: The associations of age, sex, race/ethnicity, and self-reported vascular disease history with brain morphology were examined in a cross-sectional study using multiple linear regression analyses. Sex × race/ethnicity interactions were also considered.

Setting: The Washington Heights–Inwood Columbia Aging Project, a community-based epidemiological study of older adults from 3 racial/ethnic groups (white, Hispanic, and African American) from northern Manhattan.

Participants: Beginning in 2003, high-resolution quantitative magnetic resonance (MR) images were acquired in 769 participants without dementia.

Main Outcome Measures: Relative brain volume (total brain volume/intracranial volume), ventricular volume, and hippocampus and entorhinal cortex volumes were derived manually on high-resolution MR images. White matter hyperintensities were quantified semiautomatically on fluid-attenuated inversion recovery–T2-weighted MR images.

Results: Older age was associated with decreased relative brain volume and with increased ventricular and WMH volumes. Hispanic and African American participants had larger relative brain volumes and more severe WMH burden than white participants, but the associations of these variables with age were similar across racial/ethnic groups. Compared with men, women had larger relative brain volumes. Vascular disease was associated with smaller relative brain volume and with higher WMH burden, particularly among African Americans.

Conclusions: Older age and vascular disease, particularly among African Americans, are associated with increased brain atrophy and WMH burden. African American and Hispanic subjects have larger relative brain volumes and more WMH than white subjects. Racial/ethnic group differences in WMH severity seem to be partially attributable to differences in vascular disease. Future work will focus on the determinants and cognitive correlates of these differences.

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Aging is accompanied by a diminution in brain volume and by an increase in cerebrovascular disease.\(^1\) Magnetic resonance (MR) imaging provides the capacity to visualize and to quantify these changes in vivo. Population-based and clinic-based cross-sectional and longitudinal studies have shown that normal aging is associated with decreases in total brain volume\(^2\,\(^8\) and with increases in white matter hyperintensity (WMH) burden,\(^7\,\(^11\) which appear as areas of increased signal intensity on T2-weighted MR images, including fluid-attenuated inversion recovery (FLAIR) images, and are thought to reflect small vessel vascular disease.\(^12\,\(^14\) Age-associated changes in brain volume and in WMH volume account for some degree of age-associated cognitive decline\(^15\,\(^19\) and are particularly vulnerable to the effects of vascular risk factors.\(^10\,\(^20\,\(^26\)

The population of older adults is rapidly becoming more racially/ethnically diverse,\(^22\) and the importance of including racial/ethnic minorities in aging studies is well established.\(^28\) Investigations that have examined the associations between aging and brain morphology have generally relied on small samples with limited racial/ethnic diversity.\(^11\,\(^13\) Even large community-based samples that incorporated MR imaging have been generally limited to white subjects,\(^7\) with rare exceptions.\(^20\,\(^30\) Studies\(^10\,\(^31\,\(^34\) that have included racial/ethnic minorities have

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found substantial differences in brain morphology that corresponded to differences in prevalent cardiovascular risk. However, these studies were limited to comparison of white subjects with African Americans.

The Washington Heights–Inwood Columbia Aging Project (WHICAP) is an ongoing community-based study of aging and dementia comprising older participants from an urban community. A unique aspect of the cohort is the inclusion of Caribbean Hispanics and African Americans, which facilitates the examination of race/ethnicity as a modifying factor in cognitive aging. It has previously been shown that the prevalence and incidence of cerebrovascular disease and dementia are higher among African Americans and Hispanics than among white subjects in this cohort. Therefore, it is important to examine racial/ethnic differences in brain morphology that may affect cognitive aging. In 2003, we began systematically acquiring structural MR images among active participants without dementia in the study cohort. The objective of the present study was to examine the effects of age, sex, race/ethnicity, and vascular disease history on common measures of brain morphology. Analyses focused on global atrophy (ie, total relative brain volume and ventricular volume), hippocampus and entorhinal cortex volumes, and severity of WMH.

**METHODS**

**SUBJECTS**

Data were included from 2776 individuals participating in a prospective study of aging and dementia among Medicare-eligible northern Manhattan residents 65 years and older (WHICAP II). The WHICAP II cohort represents a combination of continuing members of the WHICAP I cohort originally recruited in 1992 (n=602) and members of a new cohort recruited between 1999 and 2001 (n=2174). The sampling strategies and recruitment outcomes of these 2 cohorts have been described in detail elsewhere. The population from which participants were drawn comprises individuals from 3 broadly defined racial/ethnic categories (Hispanic, African American, and non-Hispanic white). Participants have been followed up at approximately 18-month intervals with similar assessments at each interval. Racial/ethnic group was determined by self-report using the format of the 2000 US Census. All individuals were first asked to report their race/ethnicity (American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, black or African American, or white) and then in a second question were asked whether or not they were Hispanic. Recruitment, informed consent, and study procedures were approved by the institutional review boards of Columbia University Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute, New York.

**Figure 1** shows the derivation of the WHICAP imaging sample. The imaging project was concurrent with the second follow-up of the WHICAP II cohort. Participants were deemed potentially eligible for MR imaging if they did not meet criteria for dementia at the most recent visit before the second follow-up. At the conclusion of the first follow-up, 2113 participants were considered for MR imaging eligibility; 2053 of these individuals had been seen at the first follow-up and, for 60 of these participants, their most recent visit was baseline (ie, they were not seen during the first follow-up wave). Dementia was diagnosed in 272 of these 2113 participants (12.9%). Of the remaining 1841 participants, 769 (41.8%) underwent MR imaging. As detailed in Figure 1, 407 of the remaining 1072 (38.0%) refused participation. Frequencies and specific reasons why these participants did not undergo MR imaging are shown in Figure 1.

We compared the demographic characteristics of 769 individuals who underwent MR imaging with those of 407 individuals who refused participation in the MR imaging study but otherwise met inclusion criteria (Table 1). Those who refused participation were a year older and more likely to be female. African Americans were more prevalent among those who underwent MR imaging. Education status was similar between the 2 groups. These findings were essentially identical when we compared 769 subjects who underwent MR imaging with 1072 subjects who were eligible but did not undergo MR imaging.

**SUBJECT EVALUATION**

**Clinical Evaluation**

At every assessment, each participant underwent an in-person interview regarding general health and functional ability, followed by a semistructured standardized assessment, including medical history, physical and neurologic examination, and neuropsychological test battery that constituted measures of memory, orientation, language, abstract reasoning, and visuospatial ability. The neuropsychological test battery and its validity in the diagnosis of dementia have been described in detail in a previous publication. All participants received structured neurologic, medical, and functional assessments. The diagnosis of dementia was based on standard research criteria and was established using all available information (except the MR imaging results) gathered from the initial and follow-up assessments and medical records at a consensus conference of physicians, neurologists, neuropsychologists, and psychiatrists.

**Vascular Disease History**

History of diabetes mellitus, hypertension, heart disease, and clinical stroke was ascertained by self-report. History of heart...
disease included arrhythmias (eg, atrial fibrillation), coronary artery disease, and congestive heart failure. Stroke was defined according to the World Health Organization criteria40 based on self-report, supplemented by a neurologic examination. These 4 dichotomous variables were summed to create a vascular disease history variable (score range, 0–4).

MR IMAGING PROTOCOL

Acquisition

Image acquisition was performed on a 1.5-T scanner (Philips Inntera, Best, the Netherlands) at Columbia University Medical Center, and images were transferred electronically to the University of California at Davis, Sacramento, for morphometric analysis in the Imaging of Dementia and Aging Laboratory. For measures of total brain volume, ventricular volume, and WMH volume, FLAIR-weighted images (repetition time, 11 000 milliseconds; echo time, 144.0 milliseconds; inversion time, 2800 milliseconds; field of view, 25 cm; number of signals acquired, 2; and 256×192-pixel matrix with 3-mm section thickness) were acquired in the axial orientation. T1-weighted images acquired in the axial plane and resectioned coronally were used to quantify hippocampuses and entorhinal cortex volumes (repetition time, 20 milliseconds; echo time, 2.1 milliseconds; field of view, 240 cm; and 256×160-pixel matrix with 1.3-mm section thickness).

Quantification of WMH Volume, Total Relative Brain Volume, Lateral Ventricular Volume, Hippocampus Volume, and Entorhinal Cortex Volume

Five morphologic variables were derived for the present analyses, including WMH volume, total relative brain volume (total brain volume/intracranial volume), lateral ventricular volume, hippocampus volume, and entorhinal cortex volume. User-operated image analysis was performed on a workstation (Ultra 5; Sun Microsystems, Santa Clara, California) using the Quantium 6.2 software package (Sun Microsystems). Subject identification information was not available to the operator.

Total brain and WMH volumes were derived on FLAIR images following a 2-step process, as previously described.41–42 An operator manually traced the dura mater within the cranial vault, including the middle cranial fossa but not the posterior fossa and cerebellum. Intracranial volume was defined as the number of voxels contained within the manual tracings, multiplied by voxel dimensions and section thickness. These manual tracings also defined the border between brain and nonbrain elements and allowed the removal of nonbrain elements.

Nonuniformities in image intensity were removed,43 and 2 gaussian probability functions, representing brain matter and cerebrospinal fluid (CSF), were fitted to the skull-striped image.44–45 Once brain matter was isolated, a single gaussian distribution was fitted to image data, and a segmentation threshold for WMH was set a priori at 3.5 SDs in pixel intensity above the mean of the fitted distribution of brain matter. Erosion of 2 external image pixels was applied to the brain matter image before modeling to remove partial volume effects and ventricular ependyma on WMH determination. White matter hyperintensity volume was calculated as the sum of voxels 3.5 SD or greater above the mean intensity value of the image and multiplied by voxel dimensions and section thickness. Similarly, total brain volume was the sum of voxels designated as brain volume from the segmentation process. Relative brain volume was the ratio of total brain volume to intracranial volume. White matter hyperintensity volumes were also adjusted by intracranial volume.

Lateral ventricular volumes were calculated based on previously reported methods.46 In brief, after segmentation of the image into CSF and brain matter tissue types, the operator returned to the image and outlined the ventricles according to a standardized protocol. Voxels belonging to the CSF tissue class were then counted within each region of interest and were summed across the regions of interest to form the ventricular measures.

Boundaries for the hippocampus were manually traced from the coronal 3-dimensional T1-weighted images after reorientation along the axis of the left hippocampus. While the borders were traced on the coronal sections, corresponding sagittal and axial views were simultaneously presented to the operator in separate viewing windows to verify hippocampal boundaries. The rostral end of the hippocampus was identified using the sagittal view to distinguish between amygdala and the head of the hippocampus. The axial view was used as a separate check. In anterior sections, the superior boundary of the hippocampus was the amygdala. In sections in which the uncus lies ventral to caudal amygdala, the uncus was included in the hippocampus. In more posterior sections that do not contain amygdala, the hippocampal (choroid) fissure and the superior portion of the inferior horn of the lateral ventricle formed the superior boundary. The fimbria were excluded from the superior boundary of the hippocampus. The inferior boundary of the hippocampus was the white matter of the parahippocampal gyrus. The lateral boundary was the inferior (temporal) horn of the lateral ventricle, taking care in posterior sec-

Table 1. Demographic Comparison of Participants Who Received Magnetic Resonance (MR) Imaging With Those Who Were Eligible but Refused Participation in the MR Imaging Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Refused (n=407)</th>
<th>Imaged (n=769)</th>
<th>Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>81.59 (6.36)</td>
<td>80.43 (5.63)</td>
<td>t&lt;sub&gt;1170&lt;/sub&gt;=3.10</td>
<td>.002</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>10.69 (4.78)</td>
<td>10.48 (4.89)</td>
<td>t&lt;sub&gt;1170&lt;/sub&gt;=0.72</td>
<td>.47</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>75.4</td>
<td>67.1</td>
<td>χ²=8.8</td>
<td>.003</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td>χ²=23.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>37.3</td>
<td>26.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>22.6</td>
<td>34.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>39.1</td>
<td>37.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. 92 264

African Americans

No. 159 285

Hispanics<sup>a</sup>

No. 159 285

<sup>a</sup>Four participants in the “refused” group and 15 participants in the “imaged” group self-identified ethnically as “other.” They are included in the description-comparison of the total sample, but not in any of the ethnic subgroups (ie, white, African American, or Hispanic).

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of the entorhinal cortex area was outlined on 3 consecutive 3D structural T1-weighted images of each participant. The outline continued along the surface of the entorhinal cortex from the inferomedial surface of the brain back to the starting point. This procedure was repeated using the same landmarks on the immediately adjacent rostral and caudal sections to calculate the total entorhinal area. Interrater reliabilities for this process averaged 0.90.

### Table 2. Demographic and Risk Factor Profiles Stratified by Race/Ethnicity and by Sex for Participants in the Present Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>White Subjects (n=203)</th>
<th>African Americans (n=243)</th>
<th>Hispanics (n=256)</th>
<th>Total Sample (N=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics, Mean (SD), y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>82 (121)</td>
<td>74 (169)</td>
<td>67 (189)</td>
<td>222 (479)</td>
</tr>
<tr>
<td>Age</td>
<td>79.12 (81.91, 80.25)</td>
<td>78.40 (80.29, 79.71)</td>
<td>79.77 (80.46, 80.27)</td>
<td>79.08 (80.53, 80.07)</td>
</tr>
<tr>
<td>Education</td>
<td>14.19 (13.42, 13.73)</td>
<td>12.07 (12.42, 12.31)</td>
<td>6.82 (6.88, 6.86)</td>
<td>11.26 (10.48, 10.73)</td>
</tr>
<tr>
<td><strong>Vascular Disease History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>56.1 (52.9, 54.2)</td>
<td>59.5 (74.0, 69.5)</td>
<td>64.2 (76.7, 73.4)</td>
<td>59.6 (69.7, 66.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>22.0 (9.1, 14.3)</td>
<td>20.3 (29.6, 26.7)</td>
<td>25.4 (22.2, 23.0)</td>
<td>22.4 (21.5, 21.8)</td>
</tr>
<tr>
<td>Heart disease, %</td>
<td>31.7 (22.3, 26.1)</td>
<td>24.3 (20.1, 21.5)</td>
<td>23.9 (15.9, 18.0)</td>
<td>26.9 (19.0, 21.5)</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>38.3 (30.8, 33.8)</td>
<td>47.3 (28.6, 34.3)</td>
<td>32.8 (26.6, 28.2)</td>
<td>39.6 (28.4, 31.9)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1.82 (1.29, 1.50)</td>
<td>2.12 (1.82, 1.92)</td>
<td>1.97 (1.51, 1.63)</td>
<td>1.96 (1.57, 1.69)</td>
</tr>
<tr>
<td>history score, mean (SD)</td>
<td>(1.13) (0.93, 1.05)</td>
<td>(1.12) (1.15, 1.15)</td>
<td>(1.18) (1.05, 1.12)</td>
<td>(1.14) (1.08, 1.12)</td>
</tr>
</tbody>
</table>

### Statistical Analysis

Distribution and differences across groups in demographic data and dichotomous vascular disease history variables (ie, hypertension, diabetes mellitus, heart disease, and stroke) were determined using $\chi^2$ analysis and general linear models. The associations of demographic and vascular disease history with the morphology data were examined using multiple regression analysis, with relative brain volume, lateral ventricular volume, hippocampus and entorhinal cortex volumes, and WMH volume as dependent variables. For these analyses, race/ethnicity was “dummy” coded, with white race/ethnicity as the reference group. Interaction terms (race/ethnicity × vascular disease history, race/ethnicity × age, sex × vascular disease history, and sex × age) were calculated and were included in additional multiple regression models examining relative brain volume and WMH volume. Effects of race/ethnicity and sex and their interaction on morphology were also examined using analysis of variance.

### Results

Of 769 participants with available structural MR imaging data, 52 met diagnostic criteria for dementia at the clinical evaluation closest to the neuroimaging study. These individuals were excluded from the present analyses. Because we were interested in study-
ing effects of the 3 most representative racial/ethnic groups in the cohort (ie, white subjects, African Americans, and Hispanics), we excluded 15 participants who self-identified as belonging to a different racial/ethnic group, resulting in a study sample of 702. Of these 702 participants, total brain, total ventricular, and WMH volumes were calculated in 686, hippocampus volume was calculated in 663, and entorhinal cortex volume was calculated in 555. Demographic characteristics, including vascular disease variables, for these participants are given in Table 2 and are stratified by race/ethnicity and by sex.

**RELATIVE BRAIN VOLUME**

Results of the regression analysis revealed significant effects of age, sex, vascular disease history, and race/ethnicity on relative brain volume ($F_{5,685}=38.290$, $P<.001$). For each additional year in age, there was an associated 0.3% decrease in relative brain volume ($\beta=-0.003$, $t=10.34$, $P<.001$) (Figure 2). Relative brain volume among women was 2% larger than that among men ($\beta=0.02$, $t=5.93$, $P<.001$). Hispanic ($\beta=0.03$, $t=7.20$, $P<.001$) and African American ($\beta=0.02$, $t=4.09$, $P<.001$) participants had 2.8% and 1.6% larger relative brain volumes than white subjects, respectively. Finally, for each additional vascular disease, there was a 0.5% associated reduction in relative brain volume ($\beta=-0.005$, $t=-2.70$, $P<.001$). When interaction terms were entered into the model, none were significant, demonstrating that the association of vascular disease history and age with relative brain volume did not differ across race/ethnicity or sex. Analysis of variance controlling for age and vascular disease history confirmed main effects of sex ($F_{1,685}=34.906$, $P<.001$) and race/ethnicity ($F_{2,685}=23.528$, $P<.001$) but no sex × race/ethnicity interaction ($F_{2,685}=0.167$, $P=.85$) (Figure 3).

**LATERAL VENTRICULAR VOLUME**

Findings regarding relative ventricular volume paralleled the observations with relative brain volume ($F_{5,685}=21.323$, $P<.001$). Increasing age ($\beta=0.001$, $t=7.63$, $P<.001$) was associated with larger ventricular size, but being female ($\beta=-0.005$, $t=-0.005$, $P<.001$), Hispanic ($\beta=-0.005$, $t=-4.86$, $P<.001$), or African American ($\beta=-0.002$, $t=-2.00$, $P=.046$) was associated with smaller relative ventricular volume. Vascular disease history was not significantly associated with ventricular volume ($\beta=0.001$, $t=1.81$, $P=.07$).
HIPOCAMPAL AND ENTORHINAL CORTEX VOLUMES

The regression model for hippocampal volume was not statistically significant (F\textsubscript{3,660}=0.898, P=.48). On post hoc inspection, none of the independent variables were significantly associated with hippocampal volume. Similarly, the regression analysis for entorhinal cortex volume did not reach statistical significance (F\textsubscript{3,351}=1.774, P=.12). On post hoc inspection, older age was associated with smaller entorhinal cortex volume (\(b\)standardized=-0.116, \(t=-2.71, P=.007\)).

WMH VOLUME

The regression model examining WMH volume was statistically significant (F\textsubscript{3,659}=9.489, P<.001). With increasing age, there was an increase in WMH volume (\(b=0.04, t=6.10, P<.001\)) (Figure 4). Furthermore, increased WMH volume was associated with being Hispanic (\(b=0.28, t=3.44, P=.001\)), being African American (\(b=0.36, t=4.44, P<.001\)), and having increased vascular disease history (\(b=0.09, t=2.44, P=.02\)). There were no sex differences in WMH burden (\(b=0.08, t=1.15, P=.25\)). When interaction terms were entered into the regression model, there was a significant effect for the African American \(\times\) vascular disease history interaction (\(b=0.10, t=2.11, P=.04\)), indicating that the association between increased vascular disease history and WMH burden was greatest among African Americans (Figure 5). Analysis of variance controlling for age and vascular disease history confirmed a main effect of race/ethnicity (F\textsubscript{2,684}=9.722, P<.001) and no effect of sex (F\textsubscript{1,684}=1.821, P=.99) or race/ethnicity \(\times\) sex interaction (F\textsubscript{2,684}=0.014, P=.99).

COMMENT

The present study examined the effect of age, sex, race/ethnicity, and vascular disease history on measures of cerebral atrophy, hippocampus and entorhinal cortex volumes, and WMH volume among racially/ethnically diverse older adults from an urban community. Consistent with most reports, older age was associated with increased atrophy as indexed by relative brain volume and by ventricular volume. In addition, relative brain volumes were larger among women than among men. Relative brain volumes were higher among African American and Hispanic participants than among white subjects, but the relationship between age and relative brain volume was similar across racial/ethnic groups. A history of vascular disease was associated with markers of diminished brain volume similarly in men and women and across racial/ethnic groups. Hippocampus and entorhinal cortex volumes were not associated with demographic data or history of vascular disease in this cognitively healthy group of participants. Overall, age, sex, race/ethnicity, and history of vascular disease did not seem to be related to hippocampal and entorhinal cortex volumes, although on post hoc inspection older age was associated with smaller entorhinal cortex volume. The findings are in contrast with previous studies by Raz et al\textsuperscript{50} and by Rodrique and Raz\textsuperscript{51} that demonstrated volumetric reduction with age in the hippocampus and entorhinal cortex, particularly prominent among subjects with hypertension. Our findings could be explained by the fact that variability in hippocampus and entorhinal cortex volumes may be specific to Alzheimer disease or other degenerative processes\textsuperscript{52,53} less detectable in normal aging and because our sample excluded individuals with dementia. Indeed, in a morphologic study\textsuperscript{52} of rhesus monkeys, which do not develop Alzheimer pathology, there was little effect of age on hippocampal volume. Participants in the present study who met formal criteria for dementia were excluded from the analyses. Future work will focus on whether these medial temporal lobe measures have usefulness in predicting future development of dementia or in distinguishing those with dementia from those without. The functional effect of hippocampus and entorhinal cortex volumes in this population will also be examined by determining their relationship with cognitive function in a cross-sectional study.

White matter hyperintensity volumes were associated with older age and were greater among Hispanic and African American participants than among white participants, but the relationship between age and WMH volume did not vary by racial/ethnic group. These findings are consistent with previous reports demonstrating that age is a primary predictor of WMH severity\textsuperscript{52} and that WMH burden is greater among African Americans and Hispanics.\textsuperscript{53,54} As expected, vascular disease history was associated with increased WMH severity. The relationship was strongest among African American participants. African Americans in the WHICAP cohort have a higher degree of vascular disease than white subjects, coinciding with the fact that African Americans in the WHICAP cohort, particularly men, had the highest degree of vascular disease. Our findings of increased vascular disease and WMH among African Americans and Hispanics in this northern Manhattan community suggest that cerebrovascular disease may contribute substantially to cognitive impairment in this subgroup.\textsuperscript{53,55} Future studies will examine the relative contributions of...
WMH burden and MR imaging evidence of cerebral infarction to cognitive functioning in this cohort. While many of the associations among morphology, vascular disease, and demographic data in the present study were statistically reliable, effect sizes tended to be small. The magnitude of the relationships suggests that the observed effects are subtle, but further evaluation of their functional consequences is warranted. The implications of larger relative brain volumes among racial/ethnic groups with greater vascular disease (ie, African Americans and Hispanics) and with more severe WMH need to be explored further.

A unique feature of the WHICAP cohort is that it includes participants who are underrepresented in most studies that examine brain aging. The WHICAP participants are older, come from diverse educational and socioeconomic backgrounds, and vary widely in their health status. A somewhat unexpected finding in the present study was larger relative brain volumes among racial/ethnic groups and between sexes even after age and vascular disease variables were controlled, although significantly higher relative brain volumes among women have been previously reported. Few reports have explicitly compared morphology across racial/ethnic groups. However, our finding is similar to that of 1 study that showed smaller lateral

**Figure 4.** The relationship among chronologic age, race/ethnicity, and log-transformed relative white matter hyperintensity (WMH) volume. The 3 racial/ethnic groups significantly differed in severity of WMH, but the relationship between chronologic age and relative WMH volume was similar across groups. Note that data have been grouped into 25 bins on the y-axis and 30 bins on the x-axis; the number of participants represented by each data point is indicated by its size.

**Figure 5.** Race/ethnicity × vascular disease history interaction relative to white matter hyperintensity (WMH) burden. For illustration purposes, vascular disease history was dichotomized into no vascular disease history vs any vascular disease history. African Americans with vascular disease had a disproportionately greater degree of WMH than their white and Hispanic counterparts. Error bars represent standard errors. Data presented are adjusted for age and sex.
ventricular volume among Hispanic patients with probable Alzheimer disease compared with non-Hispanic white subjects. It is important to emphasize that, despite the main effects of race/ethnicity and sex on relative brain volume, there were no interactions with age. The findings suggest that these differences are likely to have existed throughout the adult life span, although differential rates of volume change may have occurred earlier in life.

The use of racial/ethnic comparisons in biomedical research is controversial because of the possibility of the assumption of racial/ethnic biologic differences when none exist.7,5 It is important to emphasize that the rationale for racial/ethnic comparisons in this study was based on previous observations that dementia risk factors, cerebrovascular disease, and dementia are more prevalent among African American and Hispanics compared with white subjects. We believe that the racial/ethnic differences in brain structure found in our study are due to lifetime exposures that include differences in the prevalence of risk factors and socioeconomic exposures that need to be more fully characterized.

The present study is among the first to compare specific brain morphometric findings among older persons in 3 racial/ethnic groups. Because the study cohort was large, drawn from a community, and diverse along a number of dimensions, these findings are more likely to reflect the general population, in which racial/ethnic diversity is increasing. Furthermore, WHICAP participants are evaluated using comprehensive neuropsychological, medical, and behavioral assessments and are followed up longitudinally. Future work will examine the association between these MR imaging measurements and current functioning, and we will be able to evaluate their value in predicting future cognitive decline.

Despite these strengths, some weaknesses should be noted. First, although the 3 main racial/ethnic groups represented in the WHICAP imaging sample are similar for age, they vary systematically and substantially on other factors. For example, Hispanic participants have markedly fewer years of formal education than African American and white participants, which may be related to life exposures and consequently brain development. Second, as with many cross-sectional neuroimaging studies, we assume that the proportion of brain volume to intracranial volume (ie, relative brain volume) is a reflection of the amount of brain atrophy. However, despite the strong relationship between relative brain volume and chronologic age, it is possible that group effects reflect lifelong differences. We will examine this issue through examination of early life nutritional status, clinical correlates, and prediction of future and past longitudinal change.

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