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Brain Behavior Relationships amongst African Americans, Caucasians and Hispanics

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Abstract

There is increasing racial and ethnic diversity within the elderly population of the United States. While increased diversity offers unique opportunities to study novel influences on aging and dementia, some aspects of racial and ethnic research have been hampered by the lack of culturally and linguistically consistent testing protocols. Structural brain imaging is commonly used to study the biology of normal aging and cognitive impairment and may therefore serve to explore potential biological differences of cognitive impairment amongst racially and ethnically diverse individuals. To test this hypothesis we recruited a cohort of approximately 400 African American, Caucasian and Hispanic subjects with various degrees of cognitive ability. Each subject was carefully evaluated using standardized diagnostic protocols that included clinical review of brain MRI to arrive at a clinical diagnosis of normal cognition, mild cognitive impairment (MCI) or dementia. Each MRI was then independently quantified for measures of brain, WMH and hippocampal volumes by a technician blind to subject age, gender, ethnicity, race and diagnostic category. The appearance of infarction on MRI was also rated by examining neurologists. Regression analyses were used to assess associations with various MRI measures across clinical diagnostic categories in relation to racial and ethnic differences. Hispanic subjects were, on average, significantly younger and had less years of education than African Americans or Caucasians. Caucasians with dementia were significantly older than both African American and Hispanic dementia patients. Highly significant differences in MRI measures were associated with clinical diagnoses for the group as a whole after adjusting for the effects of age, gender, education, race and ethnicity. Subsequent independent analyses by racial and ethnic status revealed consistent relationships between diagnostic category and MRI measures. Clinical diagnoses were associated with consistent differences in brain structure amongst a group of racially and ethnically diverse individuals. We believe these results help to validate current diagnostic assessment of individuals across a broad range of racial, ethnic, linguistic and educational backgrounds. Moreover, interesting and potentially biologically relevant differences were found that might stimulate further research related to the understanding of dementia etiology within an increasingly racially and ethnically diverse population.

Keywords

African American; Caucasian; Hispanic; Magnetic Resonance Imaging; clinical diagnosis

INTRODUCTION

Recent census data show increasing racial and ethnic diversity within the elderly population of the United States (1). While increased diversity offers unique opportunities to study novel influences on aging and dementia, some aspects of racial and cross-cultural research have been hampered by the lack of culturally and linguistically consistent testing protocols (2). For example, epidemiological studies of racial and ethnic minorities suggest an increased prevalence and incidence of dementia (3,4) with differing risk factors (5). Despite this epidemiological evidence, other studies have found that African Americans have similar distributions of Alzheimer's disease (AD) pathology (6,7), similar correlations between hippocampal size and cognition in AD (8) and no differences in incident or prevalent dementia (9-11) leading to uncertainty regarding racial or ethnic differences in dementia prevalence, incidence or etiology.

Structural brain imaging is commonly used to study the biology of normal aging (12) and cognitive impairment, particularly with regard to morphological changes associated with the AD process (13-15). Structural imaging, therefore, may serve to explore potential biological differences underlying cognitive impairment within a group of racially and ethnically diverse individuals.

Over the last 5 years, the University of California at Davis Alzheimer's Disease Center has recruited a diverse cohort of subjects using protocols designed to enroll racial and ethnic minorities in research encompassing a broad spectrum of cognitive ability. In this report we examine the relationship between clinical diagnosis and four MRI measures commonly associated with MCI and AD dementia within this group of racially and ethnically diverse individuals.

METHODS

Participants

Subject Recruitment—All participants were persons evaluated by the University of California at Davis Alzheimer's Disease Center (UCD ADC). Approximately 71% of participants were recruited through protocols designed to enhance both the racial and ethnic diversity and spectrum of cognitive dysfunction of the sample with an emphasis on normal cognition and mild cognitive impairment (MCI). These individuals were recruited through various outreach methods such as soliciting in a community hospital lobby, a community survey, health fairs or word of mouth. The remaining 29% of the participants were recruited either by seeking an evaluation at the UCD ADC or as normal research participants (usually family members of affected individuals). Thus, while this is a sample of convenience, it nevertheless represents a concerted effort to be broadly inclusive using a variety of methods of recruitment. Regardless of recruitment source, inclusion criteria were limited to age greater than 60. Exclusion criteria included unstable major medical illness, major primary psychiatric disorder (history of schizophrenia, bipolar disorder, or recurrent major depression), and substance abuse or dependence in the last five years. All participants signed informed consent, and all human subject involvement was overseen by institutional review boards at University of California at Davis, the Veterans Administration Northern California Health Care System and San Joaquin General Hospital in Stockton, California.

Clinical Evaluation—All participants received a multidisciplinary clinical evaluation through the UCD ADC. These evaluations included detailed medical history, physical exam, and neurological exam. A physician fluent in Spanish examined subjects who spoke only Spanish. A family member or other informant in close contact with the participant was interviewed to obtain information about level of independent functioning. All subjects with

clinical evidence of cognitive impairment received diagnostic neuroimaging according to American Academy of Neurology guidelines (16). Routine dementia work-up laboratory tests were obtained for all participants.

Clinical neuropsychological evaluation using standard neuropsychological tests was given to each subject. This battery was comprised of the CERAD neuropsychological battery (17,18) (Mini-Mental State Examination, List Learning, Animal Fluency, Constructional Praxis, 15-item Boston Naming Test for Spanish speakers, 60-item version for English speakers) supplemented by WAIS-R Digit Symbol (19) and the Trail Making Test. Clinic Referral cases generally had additional neuropsychological tests performed prior to enrollment in this study including WAIS-R Block Design and Digit Span (19), WMS-R Logical Memory I and II (20), the American Version of the National Adult Reading Test (21), and the Word List Learning Test from the Memory Assessment Scales (22).

Diagnosis of cognitive syndrome (Normal, MCI, Dementia) and, for individuals with dementia, underlying etiology was made according to standardized criteria and methods. Each case was initially diagnosed at a consensus conference by the clinical team evaluating the participant. Those appearing likely to be eligible for this study were then reviewed at a second, multidisciplinary UCD ADC-wide case adjudication conference. Dementia was diagnosed using DSM-III R (23) criteria for dementia modified to exclude the requirement of memory impairment. Alzheimer's disease (AD) was diagnosed using NINCDS-ADRDA criteria (24). Vascular dementia was diagnosed using the California ADDTC diagnostic criteria for ischemic vascular dementia (25). MCI was diagnosed if the person did not meet diagnostic criteria for dementia, but performed below the 10th percentile for age and education in at least one cognitive domain in the setting of generally normal daily function according to accepted criteria (16). MCI was further subtyped according to current Alzheimer's Disease Centers Uniform Data Set guidelines (26). Normal cognitive function was diagnosed if there was no clinically significant cognitive impairment. Importantly, all subject diagnoses were made blind to research neuropsychological testing or quantitative brain image analysis. For this analysis, individuals diagnosed as having clinically probable vascular dementia, frontal-temporal dementia or dementia where the etiology was uncertain, were excluded from the study.

MRI Acquisition

Brain imaging was obtained at the University of California at Davis MRI research center on a 1.5T GE Signa Horizon LX Echospeed system or the Veterans Administration at Martinez on a 1.5 T Marconi system. Comparable imaging parameters were used at each site as follows:

1. Axial spin echo, T2 weighted double echo image with TE1 equal to 20 ms, TE2 equal to 90 ms, TR equal to 2420 ms with a field of view of 24 cm and a slice thickness of 3 mm.
2. Coronal 3D spoiled gradient recalled echo (IR-prepped SPGR) acquisition, T1 weighted image with TR equal to 9.1 ms a flip angle of 15 degrees and a field of view 24 cm and a slice thickness of 1.5 mm.
3. Axial high resolution FLAIR image with a TE1 of 120 ms a TR of 9000 ms a TI 2200 ms and 24 cm field of view with a slice thickness of 3 mm.

All available image sequences were used to assist with clinical diagnosis. Image quantification, however, was performed by a rater who was blind to age, gender, race, educational achievement, ethnicity and diagnostic status. Conversely, quantitative MRI data were not made available to the clinical diagnostic team.

Image Analysis

Brain and WMH volumes—Analysis of brain and WMH volumes was based on a Fluid Attenuated Inversion Recovery (FLAIR) sequence designed to enhance WMH segmentation (27). Images were orientated parallel to a hypothetical line connecting the Anterior Commissure (AP) and Posterior Commissure (PC).

Brain and WMH segmentation was performed in a two-step process according to previously reported methods (28,29). In brief, non-brain elements were manually removed from the image by operator guided tracing of the dura matter within the cranial vault including the middle cranial fossa, but excluding the posterior fossa and cerebellum. The resulting measure of the cranial vault was defined as the total cranial volume (TCV) and was used to correct for differences in head size amongst the subjects. Image intensity nonuniformities (30) were then removed from the image and the resulting corrected image was modeled as a mixture of two gaussian probability functions with the segmentation threshold determined at the minimum probability between these two distributions (28). Once brain matter segmentation was achieved, a single gaussian distribution was fitted to the image data and a segmentation threshold for WMH was *a priori* determined at 3.5 SDs in pixel intensity above the mean of the fitted distribution of brain parenchyma. Morphometric erosion of two exterior image pixels was also applied to the brain matter image before modeling to remove the effects of partial volume CSF pixels and ventricular ependyma on WMH determination. Intra and inter rater reliability for these methods are high and have been published previously (12).

Hippocampal volumes—Boundaries for the hippocampus were manually traced from the coronal 3D-T1 weighted images after reorientation along the axis of the left hippocampus. While the borders were traced on the coronal slices, corresponding sagittal and axial views were simultaneously presented to the operator in separate viewing windows in order 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 sections to exclude the tail of the caudate nucleus. The posterior boundary of the hippocampus was the first slice in which the fornices were completely distinct from any gray/white matter of the thalamus.

Intra-rater reliability determined for both right and left hippocampus using this method is quite good with ICCs of .98 for right hippocampus and .96 for left hippocampus.

MRI Infarctions—The presence or absence of cerebral infarction on MRI was determined according to previously published protocols (12,29). The presence of MRI infarction was determined from the size, location and imaging characteristics of the lesion based on review of the PD/T2 double echo, the FLAIR and the 3D-T1 high-resolution image. Signal void, best seen on the T2 weighted image was interpreted to indicate a vessel. Only lesions 3mm or larger qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included: 1) CSF density on T1 weighted or FLAIR image and 2) If the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels. Previously reported Kappa values for agreement amongst the three raters were generally good and ranged from 0.73 to 0.90 (12).

STATISTICS

MRI measures of WMH, brain and hippocampal volume are each known to vary in size by gender, age and disease (12-14), therefore, all MRI variables were divided by TCV in order to reduce gender differences (12). To avoid confusion, corrected brain volume is denoted as TCBV, corrected hippocampal volume is denoted as HippoN. The distribution of normalized WMH was skewed and therefore WMH data were first divided by TCV and then log transformed to better approximate a normal distribution for analysis and is designated as LWMH. Since the average of LWMH is a fraction less than 1 and the log of a fraction less than 1 is negative, mean LWMH values were negative.

Multiple regression analyses were used to examine the impact of age, gender, education, racial or ethnic status and clinical diagnoses on MRI measures. Interaction effects between clinical diagnosis and race or ethnic differences were examined whenever main effects of race or ethnicity were significant. In addition, One-way analysis of variance with Tukey *post-hoc* comparison ($p < 0.05$) was used to examine the impact of clinical diagnosis on MRI, demographic and cognitive measures according to racial or ethnic status. Chi-square analysis was used to evaluate differences amongst categorical variables.

RESULTS

Subjects

Demographics—Subject demographics are summarized in Table 1. Brain MRI and clinical diagnosis were available for 401 individuals of this study. Approximately 53% (210) of the subjects identified themselves as belonging to a minority racial or ethnic category with 26% self identified as African American and 27% self identified as Hispanic. African American and Hispanic subjects were significantly more likely to be recruited through community outreach than through clinical evaluation (chi-square= 74.6.1, $p < 0.0001$) with 92% of the African American and 86% of Hispanic subjects being recruited through community outreach as compared to 46% of the Caucasians. Approximately 64% of Hispanic subjects received their clinical evaluation in Spanish.

Review of Table 1 reveals that mean age differed significantly across racial and ethnic groups ($F=4.6$, $p = 0.01$), although differences were only significant between Caucasians and Hispanics. Educational achievement also differed significantly across racial and ethnic groups ($F=93.4$, $p < 0.0001$) with the mean level of educational achievement differing significantly between each race and ethnic group. The proportion of Females did not vary significantly across racial and ethnic groups, although the Caucasian group tended to have a more balanced gender proportion. Vascular risk differed significantly across racial and ethnic group ($F=6.2$, $p=0.002$) due primarily to mean differences between African American and Caucasian individuals. While African American and Hispanic individuals were nearly twice as likely to have a history of clinical stroke (14.1% and 13.5 % respectively) as compared to Caucasians (8.0%), the prevalence of stroke by history was low for all three groups and did not differ statistically between groups. Finally, vascular risk was significantly associated with past medical history of stroke irrespective of race or ethnicity.

Global Cognition and Activities of Daily Living—Mean age, MMSE score, functional ability and number of subjects according to clinical diagnostic category are summarized in Table 2. Cognitively impaired individuals were generally older and less well educated irrespective of racial or ethnic grouping. Multiple regression analysis found that cognitive syndrome was the single strongest predictor of MMSE (31) and Blessed Roth (32) activities of daily living performance. Mean values for MMSE and Blessed Roth activities of daily living are shown in Figure 1. Subtle effects of race and ethnicity ($F=4.3$, $p=0.02$) on MMSE were

found as well as an interaction between race and ethnicity and clinical diagnostic category ($F=3.7$, $p=0.01$). This appears to reflect slightly lower MMSE scores for the cognitively impaired Hispanic individuals, although, again, this effect is quite small in relation to the effect of clinical diagnostic category on MMSE. No racial or ethnic effects were found with Blessed Roth activities of daily living performance.

Vascular Risk and Vascular Disease—Given the increase in vascular risk burden among the African Americans, we further investigated this relationship as well as past history of stroke according to clinical diagnostic category, age, gender as well as race and ethnicity. For vascular risk, there was a main effect of race and ethnicity (again revealing that African Americans had greater prevalence of vascular risk factors), but no significant effect of clinical diagnostic category or interaction between clinical diagnostic category and race and ethnicity. This is interpreted to indicate that, while African Americans had a higher overall vascular risk factor burden, the vascular risk factor burden did not vary significantly by diagnostic category. This is supported by the fact that post-hoc one-way analysis of variance in vascular risk burden for African Americans found no significant relationship to diagnostic category ($F=2.0$, $p>0.1$). Conversely, there was a significant increase in past history of stroke associated with clinical diagnostic category, due primarily to increased likelihood of past history of stroke among individuals diagnosed with dementia ($p=0.019$). There was also a trend toward increased past history of stroke for African Americans ($p=0.08$), but there was no interaction between diagnostic category and race or ethnicity (i.e. demented individuals were significantly more likely to have a past medical history of stroke irrespective of their racial or ethnic heritage).

MCI Subtypes—MCI clinical subtyping was also available for the 121 subjects with MCI in this study. Analysis of MCI subtype found no differences associated with age, but significant differences according to vascular risk factor burden ($F=3.6$, $p=0.01$) and ethnicity and race ($\text{Chi-sq}=15.3$, $p=0.02$). Post-hoc analysis of vascular risk factors found that individuals with multiple non-memory deficits had the greatest vascular risk burden (45%, Tukey, $p<0.05$), but the other groups did not differ from one another. Examination of the distribution of MCI subtypes according to race and ethnicity revealed that African Americans were more likely to have a non-memory form of MCI (54%) as compared to Hispanic or Caucasians (19%). This is consistent with the fact that African American MCI subjects had the highest vascular risk factor burden at 37% compared to Hispanic (26%) and Caucasian (22%) MCI subjects (Tukey, $p<0.05$).

MRI

Brain and Hippocampal Volumes—Analyses examined the relation between TCBV, HippoN and LWMH according to diagnostic category, accounting for potential differences in age, gender, education, vascular risk and race or ethnicity for all subjects combined as summarized in Table 3 and graphically displayed in Figure 2. All MRI measures differed significantly by diagnostic category. For TCBV, the full model was significant ($F=23.6$, $p<0.0001$), explained 46% of the variance in TCBV and included significant main effects of age, gender, racial and ethnic status, diagnosis and vascular risk. The main effect of race and ethnicity on TCBV was due to the fact that Hispanic subjects had larger mean brain volumes (80.8%) as compared to African Americans (78.5%) and Caucasians (77.6%). There was no significant interaction between ethnic or racial group and diagnostic category (i.e. smaller TCBV was associated with cognitive impairment irrespective of race or ethnicity).

For HippoN, the full model was significant ($F=6.8$, $p<0.0001$), explained 21% of the variance in hippocampal volume and included significant main effects of diagnostic category and gender. Although there was no main effect of race and ethnicity on HippoN, there was a significant interaction between ethnic or racial group and diagnostic category on hippocampal

volume. This was due to a complex relationship between HippoN and diagnostic category, race and ethnicity described below.

Given differences in relative brain volumes amongst the three racial and ethnic groups, we explored possible causes by examining racial and ethnic differences in absolute intracranial, brain and hippocampal volumes adjusting for age, gender, education, and diagnostic category. The full model for intracranial volume was significant ($F=22.0$, $p<0.0001$), explained 38% of the variance in intracranial volume and included significant main effects of gender, education, race and ethnicity and diagnostic category. There was no significant interaction between race and ethnicity and diagnostic category. The full model for brain volume was significant ($F=19.2$, $p<0.0001$), explained 35% of the variance in brain volume and included significant main effects of age, gender and diagnostic category. Adjusted mean brain volumes were 887.4 cc for African Americans, 900.6 for Caucasians and 887.4 for Hispanics and were not significantly different by race or ethnicity. There was no significant interaction between race and ethnicity and diagnostic category. The full model for hippocampal volume was also significant ($F=12.2$, $p<0.001$), explained 28% of the variance in hippocampal volume and included significant main effects of age, gender, diagnostic category and race and ethnicity. There was also a significant interaction between racial and ethnic status and diagnostic category. Adjusted mean volumes were 3.31 cc for African Americans, 3.52 cc for Caucasians and 3.37cc for Hispanics. The interaction appears to be driven by the fact that both African American and Hispanic cognitively normal and demented subjects had smaller hippocampal volumes than Caucasians. Within the MCI groups, Hispanics particularly, but also African Americans had larger hippocampal volumes. In summary, these analyses suggest that the racial and ethnic differences in intracranial volume (head size) accounted for most of the racial and ethnic differences in TCBV noted above. Racial and ethnic differences in HippoN appear related to absolute differences in hippocampal volume, but mostly for individuals with MCI where the clinical subtypes also differ by race and ethnicity.

White Matter Hyperintensities—For LWMH, the full model was significant ($F=8.1$, $p<0.0001$), explained 22% of the variance in LWMH and included significant main effects of age, gender and diagnostic category. There were no main effects of race and ethnicity or interaction between cognitive syndrome and race and ethnicity.

Vascular risk and MRI infarction—Given ethnic and racial differences in vascular risk, we also analyzed the prevalence of cortical or subcortical infarcts detected by MRI. Overall prevalence of cortical infarction was 6% and did not vary significantly by racial or ethnic group or diagnostic category. The prevalence of subcortical infarction was 24%, consistent with previously reported prevalence of cognitively normal individuals approximately 75 years of age (12) and also did not vary significantly by racial or ethnic group or diagnostic category. The extent of vascular risk, however, was significantly associated with the presence of cortical (RR 4.6, [2.5–6.9], $p<0.0001$) and subcortical infarction (RR 3.04, [1.8–4.3], $p<0.0001$). LWMH ($p<0.0001$) volumes were significantly greater among individuals with brain infarcts on MRI even when adjusting for age, gender, race and ethnicity, history of stroke and prevalent vascular risk factors. In summary, then, vascular risk was associated with increased likelihood of stroke by history and cerebral infarction by MRI. History of stroke and cerebral infarcts on MRI were, in turn, associated with increased LWMH burden. LWMH was significantly associated with degree of cognitive impairment even after adjusting for age, gender, education, race and ethnicity, vascular risk, past history of stroke and the presence of subcortical or cortical infarcts on MRI. Given evidence that vascular risk factors may have different relations with stroke amongst various racial and ethnic groups(33) as well as the generally stochastic nature of infarction, we believe these data indicate that LWMH is the best summary measure of cerebrovascular related brain injury for this racially and ethnically diverse cohort.

MRI Measures by Race and Ethnicity—The relationship between cognitive syndrome and brain measures was further explored for each racial and ethnic group as summarized in Figure 3. Similar associations between declining TCBV and HippoN and increasing LWMH and diagnostic category were seen across all racial and ethnic groups, although there were some subtle, but notable differences. For example, the relationship between HippoN volume and diagnostic category differed according to racial and ethnic group as noted in the multivariate analysis. Review of the data suggests African Americans had slightly smaller HippoN and showed a more linear decline with increasing cognitive impairment, whereas Caucasians and Hispanics had generally larger HippoN. HippoN was substantially reduced in the presence of MCI for Caucasians, but not for Hispanics. These differences in HippoN were not explained by differences in age or gender distributions, vascular risk factor burden or LWMH suggesting that Hispanic ethnicity was uniquely associated with a different relationship between HippoN and diagnostic category even when accounting for common risk factors.

Given the differences in HippoN, diagnostic category, race and ethnicity, we further explored the potential biological relevance of this finding. We sought to clarify the relationship between cognition and HippoN by further investigating the relationship between HippoN and episodic memory performance, a cognitive test that is believed to be specific to hippocampal function. The total model was significant ($F=12.0$, $p<0.0001$) and explained 25% of the variance in episodic memory. Larger HippoN was significantly associated with better episodic memory performance. The main effects of age, gender, education, race and ethnicity were each significant, although the impact of race and ethnicity was relatively small ($F=4.2$, $p<0.02$). There was no significant interaction between race and ethnicity and HippoN supporting the notion that although there are racial and ethnic differences in HippoN, the relationship between HippoN and episodic memory performance is positive and the slope of this positive relationship does not vary according to race or ethnicity.

CONCLUSION

Analyses of MRI measures from this relatively large racially and ethnically diverse cohort revealed consistent and significant associations with clinical diagnosis similar to previously reported MRI studies of predominantly Caucasian populations (13,34,35) offering external validity to the clinical diagnostic protocols applied in this study. On average, cognitively normal individuals had greater TCBV and HippoN and lower LWMH than did cognitively impaired individuals, particularly when compared to those diagnosed as demented. While the general relationship between MRI measures and cognitive status remained when examining subjects according to racial or ethnic group, interesting differences emerged. For example, TCBV was generally larger for Hispanic subjects, independent of diagnostic category, even after correcting for differences in age, education, gender and vascular risk. This effect does not appear related to differences in severity of cognitive impairment amongst the Hispanics as all three groups were well matched on measures of functional impairment. Analysis of absolute cerebral volumes, however, did not show racial or ethnic differences like those observed for intracranial volume. That is, absolute brain matter volume did not differ across groups but intracranial volume was smaller in Hispanics, and consequently, normalized brain matter was larger in Hispanics. Head size has been linked to early life developmental influences (36), and one hypothesis to account for the observed differences in intracranial volume is that environmental and nutritional deprivation in Hispanics may have contributed to these differences. Further investigation is clearly needed, though, to both replicate our findings and to directly examine variables that might account for the differences we found.

Despite these racial and ethnic differences, the relationship between specific brain structures, diagnostic categorization and episodic memory performance remained consistent. For example, HippoN was positively associated with episodic memory performance across all three

racial and ethnic groups and the slopes of these relationships were parallel, despite mean differences in HippoN. Even though subtle racial or ethnic differences in brain structure exist, the biological relationship between regional brain size and cognition remains the same.

The impact of cerebrovascular disease on cognition for this group was complex. The presence of cerebrovascular disease and stroke is reportedly higher in African American and Hispanic community studies (33,37) and is, therefore, important to understanding racial and ethnic differences in prevalent dementia as well as differences in MRI findings. While our study found a significantly higher prevalence of vascular risk factor burden among African Americans, we did not identify any significant racial or ethnic differences in past medical history of stroke or prevalent brain infarction on MRI. This may reflect limited power to detect differences, racial and ethnic differences in reporting or detecting risk factors or racial and ethnic differences in the relation between risk factors and infarcts as previously described (33). A past history of stroke, however, was associated with increased likelihood of dementia irrespective of race or ethnicity. The finding of increased history of stroke in association with dementia is consistent with other studies that find cerebrovascular disease or stroke are associated with brain atrophy (12,38), WMH (39) and increased risk for dementia, including AD (40-42). Increased vascular risk burden, however, was associated with history of stroke and increased likelihood of MRI infarcts. MRI infarcts were also significantly associated with LWMH. Increased vascular risk burden, therefore, may explain the generally higher LWMH for African Americans (Figure 3c). In addition, further analyses of MCI subtypes showed that African Americans were more likely to have the non-memory subtype. This is consistent with the fact that the non-memory subtype of MCI was associated with higher vascular risk factor burden and lends further supporting evidence for a greater influence of vascular disease on cognition for African Americans. Racial and ethnic differences in vascular risk, therefore, seem to be expressed most strongly among non-demented individuals, whereas clinical stroke is strongly associated with dementia irrespective of race or ethnicity. As noted above, however, it may be that the prevalence of substantial vascular injury such as cortical infarctions was too low and the study group too small to detect a racial or ethnic effect. Further investigations with a larger cohort may be necessary to clarify this apparent contradiction.

MRI studies of racial or ethnic minorities with cognitive impairment are still quite limited (43-46), but tend to support expected findings with smaller hippocampi amongst individuals with dementia (43,44), although one study (46) did show smaller ventricular size amongst demented Hispanics, consistent with our finding of larger brain volumes. MRI studies of the SALSA cohort also suggest a strong relationship between cognitive status and WMH volumes (43), including memory performance (47) consistent with our results. Our findings, therefore, support the validity of clinical diagnosis in a racially, ethnically, linguistically and educationally diverse group of individuals. The data, however, also raise some interesting questions about differences in brain-behavior relationships within this diverse group as noted above.

There are, however, a number of limitations to this study. Our cohort included individuals presenting to a memory disorders clinic as well as those recruited from the community and our findings, therefore, can not be assumed to reflect the general population. Memory complaints are significantly associated with increased likelihood of dementia, even in the absence of documented cognitive impairment (48). Patients presenting to a memory disorders clinic, particularly when they have MCI, as most often occurred with the Caucasian subjects, may be even more likely to have a neurodegenerative disorder and therefore possible differences in underlying disease. Racial and ethnic differences in vascular risk factor burden and history of stroke, particularly among demented individuals hint at this possibility. Differences in native language might also contribute to differences in diagnostic accuracy, particularly when subjects are not tested in their native language. We believe that this effect was minimized by our study

methods through the use of culturally and linguistic sensitive diagnostic evaluations. The MRI results support this contention as well, because the relationship between brain measures and cognition did not differ systematically amongst the three racial and ethnic groups. Group differences in age and educational achievement also may have contributed to differences. Even with statistical correction, the prevalence of various neurodegenerative diseases are age-related and could therefore contribute differentially to the biology of cognitive impairment amongst the different racial and ethnic groups (49), although group mean age differences were relatively small. Striking differences in educational achievement are also apparent, particularly amongst the Hispanic subjects of the study, but again, degree of educational achievement did not appear to impact on the relationship between MRI measures and clinical diagnostic categorization within our cohort. Finally, while this is a fairly large cohort of minority individuals, analytical power is limited, particularly when evaluating interactions amongst diagnostic subgroups, race and ethnicity. This may explain the incongruence of the data, particularly related to the effects of vascular disease.

Despite these apparent limitations, we believe this to be one of few studies to systematically examine the relationship between a variety of MRI measures and clinical diagnoses within a racially, ethnically, linguistically and educationally diverse group of individuals. Our results suggest that linguistically appropriate clinical diagnostic protocols currently in use at our center are associated with the expected morphological brain differences of the AD process and offer convergent validity for this approach within such a broadly defined study population establishing confidence in other studies of brain behavior relationships among a racially and ethnically diverse group of individuals. Differences in associations between clinical diagnoses and brain morphology amongst the racial and ethnic groups, while subtle, may also offer new avenues for future research, particularly genetic research where MRI has recently been recognized as a suitable endophenotype (50-55) and major genetic causes of dementia may differ substantially by race (56).

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Figure 1.

a. MMSE Scores. Graphic display of MMSE scores across cognitive syndrome stratified by race and ethnicity. b. Blessed Roth Scores. Blessed-Roth disability scores across cognitive syndrome stratified by race and ethnicity.

Figure 2.

MRI Measures by Diagnosis. Graphic display illustrating brain, hippocampal and WMH measures for the entire group according to clinical syndrome. Volumes were converted to z-scores for comparison across measures. See text for details.

Figure 3.

a. Brain Volume by Diagnosis. b. Hippocampal Volume by Diagnosis. c. WMH Volume by Diagnosis. Graphic display of age related differences in brain (3a), hippocampal (3b) and log WMH volumes (3c). Hispanic subjects had higher mean volumes for age for both measures, but declined with age in a manner similar to African Americans and Caucasians. Measures are presented as percentage of head size to correct for potential differences related to gender and height. Note that the log of a fraction is a negative value. Since WMH/TCV is generally less than 1%, the log of this ratio is negative. Less negative values translate to higher WMH volumes.

Table 1

Demographics of study group

Group	N	Age (yrs) ^{¶¶}	Gender (M/F)	Education (yrs) ^{¶¶¶}	Vascular Risk (%) [¶]	English Fluency (%)	Outreach
African Americans	103	74.5 ± 6.9	34/69	13.0 ± 3.2 [0–20]	0.31 ± 0.25	99	92%
Caucasians	191	75.3 ± 7.5	82/109	14.4 ± 3.4 [8–20]	0.22 ± 0.20	99	46%
Hispanics	107	72.6 ± 7.4	33/74	7.8 ± 5.6 [0–20]	0.26 ± 0.22	36	86%

Group differences

Post-hoc analyses (p < 0.05; Tucky-Kramer, all groups comparison): Age differs significantly between Caucasians and Hispanics Education differs significantly across all groups Vascular risk differs significantly between African Americans and Caucasians

¶ p < 0.01
¶¶ p < 0.001
¶¶¶ p < 0.0001

Table 2
Age and subject numbers amongst cognitive syndromes

Group	Normal Cognition	MCI	Dementia
African Americans			
N	59	31	13
Age (yrs)	73.5 ± 7.0	75.7 ± 6.9	76.6 ± 5.6
Education [¶]	14.0 ± 2.4	11.7 ± 3.8	11.9 ± 4.1
MMSE ^{¶¶¶}	27.7 ± 2.2	25.4 ± 3.5	19.7 ± 5.1
Blessed Roth ^{¶¶¶}	0.15 ± .61	0.69 ± 0.70	3.9 ± 1.8
Caucasians			
N	70	73	47
Age (yrs) [¶]	73.8 ± 7.3	75.3 ± 7.4	77.7 ± 7.6
Education [¶]	14.5 ± 3.3	15.2 ± 3.1	13.1 ± 3.7
MMSE ^{¶¶¶}	28.9 ± 1.2	27.2 ± 1.9	21.6 ± 5.0
Blessed Roth ^{¶¶¶}	0.3 ± 0.8	1.4 ± 1.1	4.6 ± 3.2
Hispanics			
N	55	30	22
Age (yrs) [¶]	71.1 ± 6.8	72.1 ± 7.5	77.3 ± 7.0
Education	8.9 ± 5.7	7.0 ± 5.8	6.0 ± 4.4
MMSE ^{¶¶¶}	27.5 ± 2.7	22.7 ± 5.4	16.6 ± 5.8
Blessed Roth ^{¶¶¶}	0.6 ± 1.3	1.2 ± 1.1	4.2 ± 2.3

Group differences

¶¶ p < 0.001

¶ p < 0.01

¶¶¶ p < 0.0001

Table 3

MRI Analysis

Measure	Variables of Interest (F value/ P value)					
	Age	Education	Gender	Race/Ethnicity	Diagnosis	Vascular Risk
TCBV	97.7 <0.0001	0.66 0.42	14.5 0.0002	13.3 <0.0001	11.0 <0.0001	5.7 0.02
HippoN	3.8 0.05	0.27 0.60	7.3 0.008	2.5 0.09	15.7 <0.0001	0.47 0.49
LWMH	45.6 <0.0001	0.10 0.74	6.1 0.01	1.4 0.25	6.7 0.001	1.9 0.17
						0.21 0.93 3.2 0.01 0.98 0.42