Original Investigation

Association of 3.0-T Brain Magnetic Resonance Imaging Biomarkers With Cognitive Function in the Dallas Heart Study

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IMPORTANCE Understanding the relationships between age-related changes in brain structure and cognitive function has been limited by inconsistent methods for assessing brain imaging, small sample sizes, and racially/ethnically homogeneous cohorts with biased selection based on risk factors. These limitations have prevented the generalizability of results from brain morphology studies.

OBJECTIVE To determine the association of 3.0-T structural brain magnetic resonance (MR) imaging measurements with cognitive function in the multiracial/multiethnic, population-based Dallas Heart Study.

DESIGN, SETTING, AND PARTICIPANTS Whole-brain, 2-dimensional, fluid-attenuated inversion recovery and 3-dimensional, magnetization-prepared, rapid acquisition with gradient echo MR imaging at 3.0 T was performed in 1645 Dallas Heart Study participants (mean [SD] age, 49.9 [10.5] years; age range, 19-85 years) who received both brain MR imaging and cognitive screening with the Montreal Cognitive Assessment between September 18, 2007, and December 28, 2009. Measurements were obtained for white matter hyperintensity volume, total brain volume, gray matter volume, white matter volume, cerebrospinal fluid volume, and hippocampal volume. Linear regression and a best predictive model were developed to determine the association of MR imaging biomarkers with the Montreal Cognitive Assessment total score and domain-specific questions.

MAIN OUTCOMES AND MEASURES High-resolution anatomical MR imaging was used to quantify brain volumes. Scores on the screening Montreal Cognitive Assessment were used for cognitive assessment in participants.

RESULTS After adjustment for demographic variables, total brain volume (P < .0001, standardized estimate [SE] = .1069), gray matter volume (P < .0001, SE = .1156), white matter volume (P = .008, SE = .0687), cerebrospinal fluid volume (P = .012, SE = -.0667), and hippocampal volume (P < .0001) were significantly associated with cognitive performance. A best predictive model identified gray matter volume (P < .001, SE = .0021), cerebrospinal fluid volume (P = .01, SE = .0024), and hippocampal volume (P = .004, SE = .1017) as 3 brain MR imaging biomarkers significantly associated with the Montreal Cognitive Assessment total score. Questions specific to the visuospatial domain were associated with the most brain MR imaging biomarkers (total brain volume, gray matter volume, white matter volume, cerebrospinal fluid volume, and hippocampal volume), while questions specific to the orientation domain were associated with the least brain MR imaging biomarkers (only hippocampal volume).

CONCLUSIONS AND RELEVANCE Brain MR imaging volumes, including total brain volume, gray matter volume, cerebrospinal fluid volume, and hippocampal volume, were independently associated with cognitive function and may be important early biomarkers of risk for cognitive insult in a young multiracial/multiethnic population. A best predictive model indicated that a combination of multiple neuroimaging biomarkers may be more effective than a single brain MR imaging volume measurement.

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Magnetic resonance (MR) imaging has an essential role in assessing changes in brain morphology and detecting cerebrovascular disease. Longitudinal and cross-sectional studies have associated brain MR imaging measurements with an increased risk for stroke, cognitive impairment, dementia, and death.

The generalizability of results from brain morphology studies has been limited by several factors, including inconsistent methods for measuring white matter hyperintensity volume (WMHV) and cognitive function, as well as small sample sizes and restricted sample characteristics (eg, elderly participants with high vascular disease burden). Automated methods have been developed to quantify cerebrovascular insults (eg, WMHV) and cortical and subcortical brain volumes, enabling more reproducible assessment among researchers.

An important work in the Framingham Heart Study cohort has further addressed these limitations and helped to define the normal distribution of brain structural findings in the general population. Despite more recent efforts to expand the racial/ethnic diversity of that cohort, inclusion of few minorities remains a limitation on the generalizability of these findings. Therefore, we acquired 3.0-T brain MR images from the Dallas Heart Study (DHS), a large, multiracial/multiethnic, population-based study, to explore the association of structural brain measurements with cognitive function.

Methods

The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center, and all participants provided written informed consent. The DHS is a longitudinal, multiracial/multiethnic, population-based cohort study of Dallas County residents. The design of the original DHS and the details of variable definitions were described previously.

Study Population

Between September 18, 2007, and December 28, 2009, participants from the initial DHS conducted approximately 7 years prior were asked to participate in a follow-up study (DHS II). Adult family members of original participants were also enrolled in the brain imaging component of DHS II. A total of 2082 participants underwent brain MR imaging at The University of Texas Southwestern Medical Center. Family members of the original DHS participants were not included in the present study because they had not been administered cognitive testing. One hundred fourteen primarily Spanish-speaking participants who were not fluent in English were excluded. Excluded from analysis were individuals with a self-reported history of stroke (n = 42), evidence of cortical stroke or nonvascular brain pathology or surgery (n = 16), the presence of a susceptibility artifact (n = 1), acquisition error (n = 1), low signal-to-noise ratio (n = 1), and anatomical variant (n = 1). The present study included 1645 DHS participants with complete data for cognitive testing, brain MR imaging, and demographic information, including age, sex, years of education, and self-reported race/ethnicity.

Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a 30-point cognitive screening tool that requires approximately 10 minutes to administer and evaluates aspects of attention, language, verbal memory, visuospatial function, executive function, and orientation. The instrument was administered by trained personnel (H.C.R.) and double-checked for accuracy.

MR Imaging Protocol

Brain MR images were obtained on a 3.0-T MR imaging system (Achieva; Philips Medical Systems). Three-dimensional, magnetization-prepared, rapid acquisition with gradient echo images were acquired with repetition time and echo time of 9.6 and 5.8 milliseconds, respectively; flip angle of 12°; sensitivity encoding factor of 2; field of view of 260 × 260 mm; and 2-mm sections spaced at 1-mm centers. Rows times columns times sections was 288 × 288 × 140, and voxel size was 1 × 0.9 × 0.9 mm. Two-dimensional, fluid-attenuated inversion recovery images were acquired, with repetition time, echo time, and inversion time of 11 000, 130, and 2800 milliseconds, respectively; echo train length of 44; sensitivity encoding factor of 2; field of view of 250 × 250 mm; and 4-mm sections spaced at 5-mm centers. Rows times columns times sections was 560 × 560 × 32, and voxel size was 5 × 0.45 × 0.45 mm.

Exclusion criteria were applied for participant safety. These criteria included pregnancy, cochlear implant, previous brain surgery, spinal cord stimulator or other internal electrical device, cardiac pacemaker or implantable cardioverter-defibrillator, and metal fragments in the eyes, brain, or spinal canal.

Image Analysis

The following 6 morphologic variables were selected for the present analysis: WMHV, total brain volume (TBV), gray matter volume (GMV), white matter volume (WMV), cerebrospinal fluid volume (CSFV), and hippocampal volume (HCV). Quantification of MR imaging was performed using the freely available Functional MRI of the Brain Software Library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The details of the Functional MRI of the Brain Software Library tool kit used for automated segmentation were described previously.

Images were reviewed during quality control and flagged for gross abnormalities by a trained observer (M.G.) and were subsequently reviewed for exclusion by a neuroradiologist (K.S.K. and A.W.). Gross abnormalities included lesions occupying a large space, large cortical strokes, brain matter tissue loss, large metal artifacts, and processing errors.

Statistical Analysis

All brain volume measurements were calculated as raw volumes. The WMHV was not normally distributed and was log transformed for all analyses. A clear linear relationship was found between age and log-transformed WMHV. A linear relationship between the cognitive performance total score and brain MR imaging biomarkers was observed using spline interpolation of scatterplots for each of 6 identified brain regions.

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brain volumes. The presented data are adjusted for demographic factors, including age, sex, race/ethnicity, and years of education.

Linear regression was used to associate brain MR imaging biomarkers with the MoCA total score. For regression models, adjustment for demographic variables was done a priori, and all variables were entered simultaneously. A best predictive model was developed using a forward selection technique. Multiple linear regression was also used to compare individual MoCA items with brain MR imaging biomarkers. The item in each specific MoCA domain with the highest correlation with cognitive impairment was used in the multiple linear regression model.24 All testing was 2-tailed at a significance level of .05. Standardized estimate score is defined as the additional slope term added to the main MoCA slope term. Analyses were performed using statistical software (SAS, version 9.1.3; SAS Institute Inc).

Results
In total, 1645 participants were included in the study. Table 1 lists the demographic information, neuroimaging characteristics, and cognitive scores for the cohort. First-order relationships are also provided in eTable 1 in the Supplement.

Association of MR Imaging Brain Measurements With the MoCA Total Scores
The MoCA performance differed significantly with all unadjusted brain MR imaging volume measurements (eFigure in the Supplement). Except for WMH burden, this relationship persisted when adjusting for demographic variables (Table 2). A best predictive model identified GMV (P < .001, standardized estimate [SE] = .0021), CSFV (P = .01, SE = .0024), and HCV (P = .004, SE = .1017) as 3 brain MR imaging volumes significantly associated with the MoCA total score.

Interaction testing was performed to determine the effect of demographic variables on the association of brain MR imaging biomarkers with cognitive performance (eTable 2 in the Supplement). Previous work has shown that atrophy seems to accelerate at approximately age 50 years, which is when early neurodegeneration may first begin (K.S.K., unpublished data, October 2014). In addition, prior work determining normative data for the MoCA found that variance for the MoCA total scores was greatest in individuals with 12 years of education or less.25 Years of education had a significant interaction on the association of all brain MR imaging biomarkers (except for WMH burden) with cognitive performance. The association of CSFV with cognitive performance had a significant interaction with male sex. Other demographic variables, including age older than 50 years and race/ethnicity, had no significant interaction with any of the brain MR imaging biomarkers.

Association of Brain MR Imaging Volume Measurements With Specific Cognitive Domains
Table 3 summarizes the association of MR imaging brain volume measurements with specific cognitive domains as measured by the MoCA. First-order relationships are also provided in eTable 3 in the Supplement. The domain most strongly correlated with individual brain morphologic volumes was visuospatial function. Orientation had a significant interaction with only HCV. The TBV and WMV were associated with all individual domains except for verbal memory and orientation, while HCV was associated with all individual domains except for language and executive function.

### Table 1. Demographic, Neuroimaging, and Cognitive Performance Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (N = 1645)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, No. (%)</td>
<td>979 (59.5)</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>791 (48.1)</td>
</tr>
<tr>
<td>White</td>
<td>607 (36.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>247 (15.0)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>49.9 (10.5)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>12.8 (2.0)</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment total score, mean (SD)</td>
<td>23.8 (3.4)</td>
</tr>
<tr>
<td>Volume, mean (SD), mL</td>
<td></td>
</tr>
<tr>
<td>White matter hyperintensity</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Total brain</td>
<td>828 (30)</td>
</tr>
<tr>
<td>Gray matter</td>
<td>422 (35)</td>
</tr>
<tr>
<td>White matter</td>
<td>410 (30)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>172 (30)</td>
</tr>
<tr>
<td>Hippocampal</td>
<td>7 (1)</td>
</tr>
</tbody>
</table>

### Table 2. Association of Magnetic Resonance Imaging Brain Volumes With the Montreal Cognitive Assessment Total Score Among 1645 Patients

<table>
<thead>
<tr>
<th>Volume</th>
<th>Unadjusted</th>
<th>Adjusteda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE</td>
<td>P Value</td>
</tr>
<tr>
<td>White matter hyperintensity²</td>
<td>-0.0853</td>
<td>.0005</td>
</tr>
<tr>
<td>Total brain</td>
<td>0.2154</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.2948</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White matter</td>
<td>0.1159</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>-0.0579</td>
<td>.0176</td>
</tr>
<tr>
<td>Hippocampal</td>
<td>0.0827</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviation: SE, standardized estimate.
a Adjusted for age, sex, years of education, and race/ethnicity.
b Log transformed.
Brain MR Imaging Biomarkers and Cognitive Function

Discussion

Our findings support and augment the association of cognitive performance with global measures of brain volume seen in previous imaging studies,8,10,11 performed among large populations. Traditionally, biomarkers of global cerebral atrophy have been considered late-stage disease changes.26 Our results in a young population (mean [SD] age, 49.9 [10.5] years; age range, 19-85 years) suggest a link between brain volumes and cognitive function earlier in the life span. While the associations of individual brain MR imaging volumes with the MoCA total score are significant, the magnitude of the associations was small, underscoring the importance of other known factors on cognitive performance, including age and years of education.

The association of WMHV with global and domain-specific cognitive scores was attenuated when controlled for demographic factors. The results of some studies77-78 have suggested that a critical threshold for WMHV has clinical significance on cognitive function. This threshold is generally approached in elderly populations with comorbid conditions, such as hypertension and diabetes mellitus. We hypothesize that the lack of association of WMHV with cognitive performance in our study is due to low WMH burden in a young, healthy population,79 as well as the inherent limitations of a brief cognitive screening instrument.

The present study addresses a major limiting factor in population-based studies by including a large multiracial/multiethnic cohort. The importance of gathering large sample size data on a racially/ethnically diverse population to determine whether these associations are generalizable has been documented.14,15,30-32 Our findings indicate that race/ethnicity does not significantly interact with the association of brain morphologic variables with neuropsychological test results, supporting its use in a diverse population. We believe that our study provides a major contribution to the current literature given the few population-based studies15,31,32 with a large multiracial/multiethnic cohort. The generalizability of brain morphology study results has been hampered by the lack of a standardized method for brain volume measurements, particularly WMHV. While we do not solve this dilemma, we have devised an automated algorithm that can be used to assess white matter disease in a large population with a range of WMHVs. The algorithm produces results that agree with quantitative readings of WMHV by trained professionals (K.S.K. and A.W.).

Another unique feature of the present study is the identification of a statistical set of variables that best predict, and possibly underlie, cognitive outcomes. Prior literature has focused primarily on the associations of individual structural brain MR imaging measurements with cognitive function,4,7,10,13,14 but it is uncertain if these associations are independent of other brain changes. Furthermore, the data are often from small samples with a limited diversity of age range or race/ethnicity. In our best predictive model, the set of brain volume measurements most strongly associated with cognitive scores comprised GMV, HCV, and CSFV. This finding emphasizes the importance of incorporating multiple measures of brain volumes in evaluating cognitive performance rather than a single biomarker. For example, while previous studies6,8,34,35 have shown that low HCV is associated with low MoCA total scores, our study findings suggest that research should alternatively focus on the additive effect of GMV, CSFV, and HCV to determine the full extent of the association of brain volume loss with cognitive performance.

The MoCA measures 6 cognitive domains of attention, language, verbal memory, visuospatial function, executive function, and orientation.18 While data have supported the association of brain volume measurements with the MoCA total score,13,35-37 research on domain-specific information has been heterogeneous.38,39 Our findings support the expected association of HCV with the verbal memory domain of the MoCA.6,8,34-35 In addition, HCV was a strong predictor of attention, visuospatial function, executive function, and orientation, supporting its importance in the development of mild cognitive impairment and overt dementia. The MoCA is considered a better predictor of vascular dementia4,35 than other brief screening measures because of its greater emphasis on visuospatial function and executive function. Our results indicate that the visuospatial domain of the MoCA has the most statistically significant correlations with individual brain MR imaging biomark-

<table>
<thead>
<tr>
<th>Volume</th>
<th>Total Score</th>
<th>Attention</th>
<th>Language</th>
<th>Verbal Memory</th>
<th>Visuospatial Function</th>
<th>Executive Function</th>
<th>Orientation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE  P Value</td>
<td>SE  P Value</td>
<td>SE  P Value</td>
<td>SE  P Value</td>
<td>SE  P Value</td>
<td>SE  P Value</td>
<td>SE  P Value</td>
</tr>
<tr>
<td>White matter hyperintensity</td>
<td>0.0120 .5975 0.0225 .4098 ~0.0105 .6829</td>
<td>~0.0350 .1718 0.0139 .5776 ~0.0016 .9468 0.0062 .8202</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brain</td>
<td>0.1069 &lt;.0001 0.0788 .0140 0.1218 &lt;.0001</td>
<td>~0.0427 .1553 0.0962 .0010 0.0952 .0009 0.0046 .8868</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>0.1156 &lt;.0001 0.0464 .1346 0.0876 .0027</td>
<td>~0.0087 .7636 0.1084 .0001 0.0946 .0007 0.0092 .7652</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td>0.0687 .0075 0.0765 .0142 0.1078 .0002</td>
<td>~0.0524 .0732 0.0589 .0385 0.0668 .0170 0.0001 .9985</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>~0.0670 .0123 ~0.0008 .9802</td>
<td>~0.0120 .6961 ~0.0722 .0076 0.0589 .0385 ~0.0391 .1803 ~0.0112 .7296</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal</td>
<td>0.0922 &lt;.0001 0.0733 .0076 0.0444 .0876</td>
<td>0.0509 .0481 0.0833 .0009 0.0272 .2699 0.0647 .0180</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviation: SE, standardized estimate.
* Adjusted for age, sex, years of education, and race/ethnicity.
† Log transformed.
ers, indicating that perhaps in our young population, brain MR imaging volumes may be better predictors of decline in cognitive performance due to vascular-related insults.

Unique aspects of the DHS include the use of 3.0-T MR imaging in a young, healthy population from diverse educational and socioeconomic backgrounds who have varied health status and a wide range of cardiovascular disease risk factors. A limitation of the present work is that only cross-sectional associations of brain volumes with cognitive testing were evaluated. We were unable to assess causality or longitudinal changes.

Our study supports global brain volume measurements as biomarkers of an increased risk for cognitive impairment well before clinical symptoms are likely evident. It addresses many of the limitations in the current literature by providing a large, young, multiracial/multietnic, population-based cohort. Longitudinal evaluation of brain volumes and the development of cognitive impairment is necessary to further characterize its usefulness in treatment trials and risk stratification.

Conclusions
Brain MR imaging volumes, including TBV, GMV, CSFV, and HCV, were independently associated with cognitive function in our young cohort and may be important early markers of risk for cognitive insult. A best predictive model indicated that a combination of multiple brain MR imaging biomarkers may be more effective than single measurements in understanding the association of brain morphologic variables with cognitive performance. Our results suggest that these associations may be generalizable to a diverse population.

REFERENCES


