Hippocampal Atrophy Correlates With Clinical Features of Alzheimer Disease in African Americans

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Context: Imaging measurements may aid in the characterization and diagnosis of patients with Alzheimer disease (AD). Most research studies, however, have been performed on predominantly white study groups despite the fact that there may be biological differences in AD between African American and white patients.

Objective: To measure hippocampal volume in African American patients with AD and to correlate these measurements with the presence of AD and neuropsychological test performance.

Design: Survey study.

Setting: Academic center.

Participants: Fifty-four healthy African American subjects and 32 African American patients with AD were studied. Hippocampal volumes were measured in all subjects from magnetic resonance images using established methods.

Main Outcome Measure: Correlations were assessed between hippocampal volume and demographic variables, clinical group membership, and neuropsychological performance.

Results: The hippocampi of patients were atrophic with respect to those of healthy subjects \((P < .01)\). Significant direct correlations were present between hippocampal volumes and performance on several different neuropsychological tests \((r > 0.5\) and \(P < .01\) for every test evaluated) when patients and healthy subjects were combined.

Conclusions: Hippocampal atrophy is a feature of AD in African Americans as it is in white subjects. The neuropsychological–hippocampal volume correlations indicate that hippocampal volume measurements do represent a measure of the structural substrate of functional impairment in AD.

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IMAGING measurements are being used with increasing frequency to aid in the characterization and diagnosis of patients with dementia, particularly Alzheimer disease (AD). One of the more widely used techniques has been volume measurements of medial temporal lobe structures, particularly the hippocampus.1-6 Hippocampal volume measurements are an appealing early diagnostic marker because the medial temporal lobe is the area of the brain where pathologic characteristics of AD typically first appear. Additionally, the boundaries of the hippocampus are reliably depicted with modern magnetic resonance imaging (MRI), lending a high degree of precision to this measurement.7 Magnetic resonance imaging measurements of hippocampal atrophy correlate with clinical measurements of disease severity, pathologic disease stage, neuropsychological performance, and disease progression.8-11 However, most research studies have been performed largely in white populations. This may be problematic because there may be biological differences in AD in African American and white patients. For example, Hendrie et al12 have reported that the incidence of AD is increased in African Americans, and some studies have shown that a difference in the apolipoprotein E (APOE) 4 genotype is a risk factor for AD in African American compared with white patients.13,14 It is important to the monitoring of treatment trials of serial hippocampal volumes that researchers establish that African Americans with probable AD have hippocampal atrophy, and that this atrophy correlates with neuropsychological testing. The purpose of this study was to measure hippocampal volumes in healthy African American subjects and African American patients with AD and to correlate these measurements with the presence of AD and neuropsychological test performance.
SUBJECTS AND METHODS

SUBJECTS

All studies were performed with Mayo Clinic institutional review board approval and informed consent of the subject and/or an appropriate surrogate. Healthy African American subjects were recruited by requesting volunteers at presentations made by one of us (P.B.W.) at churches, social and civic clubs, retirement centers, and labor union halls in Jacksonville, Fla. To take part in the study, patients had to live independently in the community, and a person who knew them well had to confirm that their memory had not deteriorated and did not interfere with their functioning. Their physicians completed a medical form indicating that the patient did not have ongoing neurological or medical illnesses that would affect their cognition. These illnesses included epilepsy, cerebrovascular disease, movement disorder, multiple sclerosis, human immunodeficiency virus infection, alcohol abuse, central nervous system infection, anoxic episodes, brain trauma with loss of consciousness, brain surgery, poisoning, hypoglycemia, ongoing psychiatric illness, and uncontrolled hypertension. A psychometrist completed a medication list, family history, demographic form, and full neuropsychological examination. These healthy subjects were followed up annually, and on alternate years we administered an interim history form and a “step-down” neuropsychological battery. If the person’s Mattis Dementia Rating Scale decreased by 10 points, the subject was offered a full neurological examination.15,16 A total of 294 healthy subjects were recruited, and a subset of 54 subjects volunteered for the MRI component of the study.

Patients with AD were recruited from a set of African American patients seen for dementia evaluation at Mayo Clinic Jacksonville under the auspices of the Mayo Alzheimer’s Disease Research Center. This is an ongoing longitudinal study of aging and dementia. After a complete neurological, neuropsychological, and laboratory evaluation, a consensus meeting was held, and the patient was given a diagnosis. Those meeting DSM-III criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Associations (NINCDS/ADRDA) criteria for probable and possible AD were included in this MRI volumetric study.17,18 Disease severity in patients with AD was assessed by the Clinical Dementia Rating (CDR) scale (very mild, CDR 0.5; mild, CDR 1; moderate, CDR 2).19 An important distinction was made between establishing a diagnosis of AD and ranking its severity. The former was done according to NINCDS/ADRDA criteria, which emphasize a decline in cognitive performance over time. The CDR score was used as a staging instrument to rank disease severity at a specific point in time. It was therefore possible for patients to meet NINCDS/ADRDA criteria for AD and also be ranked as having only very mild dementia (CDR 0.5).

Patients and healthy subjects underwent a neuropsychological testing battery, including indices of general cognitive function, the Mattis Dementia Rating Scale, Mini-Mental State Examination,15,20 and multiple memory measures, including a list-learning procedure (Auditory Verbal Learning Test), paragraph recall (Wechsler Memory Scale–Revised: Logical Memory), and nonverbal memory measures (Wechsler Memory Scale–Revised: Visual Reproductions).11,22 The median elapsed time between the date of the MRI scan and the reference date for clinical assessment was 0.12 months (range, 0–3 months) for patients and 8.4 months (range, 0–14 months) for healthy subjects.

MRI METHODS

All subjects’ hippocampi were imaged at 1.5 T using a standardized imaging protocol. The first sequence was a spinecho T1-weighted sagittal set of images that was used to measure total intracranial volume. The other pulse sequence relevant to this report was a T1-weighted 3-dimensional volumetric spoiled gradient echo sequence with 124 contiguous partitions, 1.6-mm slice thickness, 22 × 16.5-cm field of view, 192 views, and a 45° flip angle. Volume measurements of the hippocampus were derived from this pulse sequence. The image data were stored at the site of acquisition (Jacksonville) and transferred electronically to Rochester, Minn, where the image analysis was performed.

IMAGING PROCESSING

All image processing steps were performed by the same research fellow (D.S.) who was blinded to all clinical information. The 3-dimensional MRI data were interpolated in the slice-select dimension to give cubic voxels, and interpolated implant to the equivalent of a 512 × 512 matrix. The voxel size of the fully processed image data was 0.316 mm³. The borders of the hippocampi were manually traced sequentially with a mouse-driven cursor on each slice from the posterior to anterior. The number of voxels in each anatomical region of interest was counted automatically using a summed region of interest function, and then multiplied by voxel volume.

On a plane, hippocampal anatomic boundaries were defined to include the CA1 to CA4 sectors of the hippocampus proper, the dentate gyrus, and the subiculum.21 The posterior boundary of the hippocampus was determined by the oblique coronal anatomic section in which the crura of the fornices were identified in full profile. Intracranial volume was determined by tracing the margins of the inner table of the skull on contiguous images from the sagittal spin echo T1-weighted sequence.

STATISTICAL METHODS

The right and left hippocampal volumes in each subject were summed. This summed hippocampal volume was divided by total intracranial volume (ie, normalized) to control for intersubject variation in head size.15 Associations between normalized hippocampal volumes and cognitive test scores were evaluated with Spearman rank correlation analysis. The χ² test was used to test for intergroup differences in sex and APOE status. The rank sum test was used to test for intergroup differences in raw and normalized hippocampal volumes, age at MRI scan, educational attainment, and intracranial volume.

RESULTS

Demographic information for patients and healthy subjects is presented in Table 1. Eighty-six subjects were studied (54 healthy subjects and 32 patients with AD). More women than men were present in both the patient and control groups. The proportion of men was greater in the patient than in the control group (χ², P = .04).
Healthy subjects, on average, were younger than patients, (rank sum test, P < .001). On average, healthy subjects had greater educational attainment than patients (rank sum test, P = .003). The proportion of subjects with APOE genotypes known to increase risk for AD (APOE 3/4 or APOE4/4) was greater in patients than in healthy subjects (χ², P = .001). The performance of healthy subjects on general measures of cognition (Mini-Mental State Examination and Mattis Dementia Rating Scale) was better than the performance of patients. Eighteen of the patients with AD had very mild or mild disease severity (CDR 0.5 or 1, respectively), and 14 patients had moderate disease severity (CDR 2 or 3).

The hippocampi of patients were atrophic with respect to those of healthy subjects (Table 1). This was true both for raw unnormalized hippocampal volumes, as well as normalized hippocampal volumes (rank sum test, P < .001 for both). Total intracranial volume was not different between groups. Normalized hippocampal volumes declined with greater disease severity among subjects with AD; however, the association between CDR score and hippocampal volume was not significant. The presence of APOE4 was associated with smaller normalized hippocampal volumes (ie, greater hippocampal atrophy) when patients and healthy subjects were combined (rank sum test, P = .02). However, no significant association was seen between hippocampal volume and APOE4 among either patients or healthy subjects when this association was analyzed separately by group. No association was present between sex and normalized hippocampal volume among patients, healthy subjects, or the combined groups. No association between normalized hippocampal volume and age was found in either the patient or control groups.

The relationships between hippocampal volume and cognitive performance are presented in Table 2. Spearman rank correlation coefficients and associated P values when P < .2 are reported. P = .05 was considered significant, and a P value between .05 and .2 was considered “nearly significant” or “of interest.” Associations between neuropsychological performance and hippocampal volume in healthy subjects were minimal. Several of the neuropsychological tests evaluated showed a near-significant association with hippocampal volume in patients; however, the magnitude of the correlation was typically modest (ie, r < .4). When patients and healthy subjects were combined, highly significant correlations (P < .001 for all) were present between every neuropsychological test and hippocampal volume.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Subjects (n = 54)</th>
<th>Patients (n = 32)</th>
<th>Healthy Subjects and Patients (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>0.17 (. . .)</td>
<td>0.18 (. . .)</td>
<td>0.59 (&lt; .01)</td>
</tr>
<tr>
<td>Dementia Rating Scale total raw score†</td>
<td>0.05 (. . .)</td>
<td>0.04 (. . .)</td>
<td>0.52 (&lt; .01)</td>
</tr>
<tr>
<td>Auditory verbal learning test, total learning‡</td>
<td>0.19 (19)</td>
<td>0.24 (19)</td>
<td>0.60 (&lt; .01)</td>
</tr>
<tr>
<td>Auditory verbal learning test, 30-min delayed recall§</td>
<td>0.14 (. . .)</td>
<td>0.12 (. . .)</td>
<td>0.52 (&lt; .01)</td>
</tr>
<tr>
<td>Wechsler Memory Scale–Revised, logical memory II</td>
<td>0.03 (. . .)</td>
<td>0.34 (.06)</td>
<td>0.54 (&lt; .01)</td>
</tr>
<tr>
<td>Wechsler Memory Scale–Revised, logical memory III</td>
<td>0.04 (. . .)</td>
<td>0.34 (.07)</td>
<td>0.56 (&lt; .01)</td>
</tr>
<tr>
<td>Wechsler Memory Scale–Revised, visual reproductions ¤</td>
<td>0.18 (. . .)</td>
<td>0.05 (. . .)</td>
<td>0.58 (&lt; .01)</td>
</tr>
<tr>
<td>Wechsler Memory Scale–Revised, visual reproductions ¦</td>
<td>0.04 (. . .)</td>
<td>0.25 (.19)</td>
<td>0.53 (&lt; .01)</td>
</tr>
</tbody>
</table>

*Values are given as Spearman rank correlation coefficient r (P value) between normalized hippocampal volume and cognitive test score. Ellipses indicate a P value that was not significant or near significant (ie, < .2).
†One missing for patients.
‡Two missing for patients; 4 missing for healthy subjects.
§Six missing for patients; 4 missing for healthy subjects.
||Two missing for patients; 3 missing for healthy subjects.
¶Three missing for patients; 3 missing for healthy subjects.
#Four missing for patients; 3 missing for healthy subjects.
chological test evaluated and hippocampal volume; in addition, the magnitudes of the correlations were respectable (ie, r > 0.5) for every test.

Imaging is being used with increasing frequency as an aid in diagnosis and characterization of AD and other demting conditions. However, nearly all published studies have been performed in largely white populations. In this study, all members of both the patient and control groups were African American. This eliminates differences in racial composition between the control and patient groups as a possible confounder when analyzing the hippocampal volumes and AD.

Both patient and control groups were composed largely of women. Although a bias toward greater survivorship among women with advancing age exists in the general population, the high proportion of women in both groups of our study means that our data are not completely representative of the African American population as a whole in this age group. The proportion of men was greater in the patient than the control group. We do not suspect that this resulted in significant confounding of the comparison of hippocampal volumes between patients and healthy subjects because no sex differences were present in normalized hippocampal volumes among patients, healthy subjects, or in both groups combined.

On average, the level of educational attainment was lower in the patients than in the healthy subjects in this study. Rank correlations between hippocampal volume and education were not significant among healthy subjects, patients, or in both groups combined. It is unlikely, therefore, that differences in educational attainment between the patient and control groups confounded the comparison of hippocampal volumes between groups. Differences in education may, however, have affected the neuropsychological performance characteristics of the patient vs control group, and they may have also played a role in the clinical diagnosis of subjects as either patients or healthy subjects. In most studies in white populations, brain volumes, including those of the hippocampus, decline with advancing age. On average, patients were 7 years older than healthy subjects in our study. This age difference might be expected to introduce bias toward larger hippocampal volumes in healthy subjects vs patients. However, for reasons that are not entirely clear, no relationship between hippocampal volume and age was found in either the patient or control group. Therefore, the age difference between the patients and healthy subjects may not represent a significant confounding effect when comparing hippocampal volumes between the patient and control groups. Part of the explanation for the absence of an association between age and hippocampal volume in this study could be the small sample size and the restricted age range in both the patient and control groups. Of 32 patients, all but 4 were between 74 and 89 years of age. This is not a wide age range, and equally important, the sample size was small. Of 54 healthy subjects, all but 3 were between 65 and 85 years of age. Furthermore, because the healthy subjects were volunteers, there may have been a healthy volunteer bias par-ticularly in the older group, resulting in some masking of the effects of normal aging.

A final potential confounding effect was the fact that the duration between the MRI scan and the reference clinical test date was greater in healthy subjects than in patients. The greater time lapse between MRI scan and clinical assessment should make the MRI less representative of the clinical condition of the subject at the time the clinical data were acquired. By definition, patients with AD were declining both cognitively and with respect to hippocampal volumes at a greater rate than healthy subjects. The fact that this interest difference was greater in healthy subjects should not create significant data analysis problems, as healthy subjects (unlike patients) are relatively stable both cognitively and with respect to hippocampal volumes.

The major finding in this study was that hippocampal volumes were significantly atrophic in African American patients with AD compared with African American healthy subjects. This finding matches those of reports from several different centers, including our own, on white subjects. In addition, normalized hippocampal volumes declined with increasing CDR score in patients, although this association was not significant. These findings indicate that hippocampal atrophy is a feature of AD in African Americans, as is true in white subjects. This imaging measurement, therefore, has potential use as an aid in diagnosis, characterization, and measurement of disease severity in African American subjects. The use of serial hippocampal volume or other MRI-based brain measurements as a surrogate outcome measure in therapeutic trials has been proposed. Although we do not have serial measurement data permitting an assessment of the difference in rate of hippocampal volume loss between African American patients and healthy subjects at this point, our cross-sectional data demonstrating significant patient vs control group differences in hippocampal volumes lend support to the notion that MRI measurements might be a useful surrogate outcome measure for therapeutic trials in African American subjects.

The difference in the proportion of subjects who were carriers of APOE genotypes that are known to confer increased risk of AD (ie, APOE3/4 or APOE4/4) was greater in African American patients than healthy subjects (P < .01). Hippocampal volumes in APOE4 carriers were smaller than those of noncarriers when the patient and control groups were combined. However, we believe that this association simply demonstrates the fact that patients share both characteristics (ie, hippocampal atrophy and a higher prevalence of APOE4). The fact alone that no association was present between hippocampal volume and APOE4 status among patients or healthy subjects implies an absence of any cause and effect relationship between APOE4 and atrophy. This finding is identical to that observed in a larger study of white subjects.

Correlations between hippocampal volume and cognitive measures were minimal in the control group. Several nearly significant correlations were present among patients; however, in general the strength of the associations were modest. Highly significant correlations with respectable magnitudes were only seen when the patient and control groups were combined. This scenario
matches precisely what we found when performing a similar analysis in a larger group of white subjects. 9 We conclude from these data that in African American subjects under conditions of normal aging, the relationship between hippocampal volume and neuropsychological performance is negligible. The restricted range of variation in both hippocampal volumes and cognitive performance indices in the AD group probably limits the strength of the correlations observed among patients with AD only. However, when healthy subjects and AD patients were combined, a much broader range of variability existed, both in hippocampal volume and in cognitive performance. It was under these circumstances that the correlations became highly significant. We interpret these data to indicate that hippocampal volume measurements do represent a measure of the structural substrate of functional impairment due to the presence of AD pathology in African American patients.

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REFERENCES