Hippocampal Volume and Incident Dementia in Geriatric Depression

David C. Steffens, M.D., M.H.S., Martha E. Payne, M.P.H., R.D.
Daniel L. Greenberg, B.S., Christopher E. Byrum, M.D.
Kathleen A. Welsh-Bobmer, Ph.D., H. Ryan Wagner, Ph.D.
James R. MacFall, Ph.D.

The authors investigated the role of baseline hippocampal volume on later clinical emergence of dementia in a group of older, non-demented depressed individuals. Subjects were 115 depressed, non-demented participants in a mental health clinical research center. All subjects were screened for dementia and agreed to have a magnetic resonance imaging (MRI) brain scan at baseline. Subjects were clinically evaluated by geriatric psychiatrists quarterly for up to 5 years and received annual neuropsychological testing. Bivariate analyses examined age, gender, race, educational level, baseline depression severity, age at depression onset, baseline Mini-Mental State Exam (MMSE), left and right hippocampal volume, and total cerebral volume. Age, baseline MMSE, total cerebral volume, and having a small left hippocampal volume were associated with later dementia and were included in subsequent survival analysis. Small left hippocampal volume was significantly associated with later dementia (hazard ratio = 2.762). Small left hippocampal size on neuroimaging may be a marker for dementia in depressed patients who have not yet met criteria for a clinical diagnosis of a dementing disorder. (Am J Geriatr Psychiatry 2002; 10:62–71)

The relationship between geriatric depression and dementia and the possible role of the hippocampus in these disorders is poorly understood. There is growing evidence linking depression with subsequent development of dementia. Studies have shown that a previous history of depression is associated with increased risk of Alzheimer disease (AD). Individuals with late-life depression who have cognitive impairment as part of their symptomatology frequently are diagnosed with dementia within a few years after the presentation of their depression, which suggests that late-life depression may represent a prodrome of dementia. A longitudinal, prospective study followed 849 community-dwelling individuals with varying degrees of cognitive impairment (none, mild, or moderate) for 1 to 5 years to determine incident dementia and found that depressed mood at baseline was associated with a nearly threefold increased risk of incident dementia. Among elderly twins, previous depression increased the risk of later AD independent of apolipoprotein-E (ApoE) genotype. In this study, risk ratios declined substantially as the interval between onset of depression and onset...
of AD increased, suggesting that, for many individuals, the association of depression and AD may reflect the occurrence of prodromal dementia, rather than a true risk relationship. In a large metaanalysis, Jorm et al.\(^2\) found that a history of depression was associated with onset of AD after age 70 only if depressive symptoms had appeared within 10 years before the onset of dementia. However, depression with onset more than 10 years before dementia was associated with onset of AD at any age, implicating depression as a risk factor for dementia, rather than merely representing a prodromal syndrome of a dementing illness. A reanalysis\(^10\) of the studies from Jorm’s metaanalysis that included information on family history of dementia concluded that a lifetime history of depression increased the risk of AD, controlling for family history. This finding suggests that previous occurrence of depression may influence risk independent of any genetic diathesis toward AD.

At odds with the notion of depression being a risk factor for later dementia are the results from Chen et al.,\(^11\) in which 954 individuals without dementia were followed for development of depression symptoms and cognitive decline. They found that depression manifested itself early after onset of dementia and, more specifically, of AD. Depression did not increase risk of AD or of dementia. The authors concluded that depressive symptoms may be more of an early manifestation than a predictor of dementia.

One brain structure that may mediate the relationship between depression and dementia is the hippocampus. It is well established that the hippocampus is involved in memory and is significantly affected in disorders of memory such as AD.\(^12\) The role of the hippocampus in affective disorders remains unclear.\(^13\) In a series of reports, Sheline et al.\(^14\) found an association between degree of hippocampal volume reduction and total duration of major depression and found that among women ages 23–86, those with a history of depression had smaller hippocampal volumes bilaterally than control subjects.\(^15\) More recently, our group\(^13\) found smaller hippocampal volumes among older depressed patients than among elderly control subjects.

In the present study, we sought to extend these previous findings by examining the relationship between baseline hippocampal volume and later clinical emergence of dementia in a group of non-demented elderly depressed patients. We hypothesized that at baseline, depressed subjects with smaller hippocampal volumes would have higher incident dementia, controlling for age, gender, education, and total brain volume, and that the relationship would remain predictive independent of ApoE genotype. Also, we aimed to examine whether there were any lateralizing findings, given previous reports that geriatric depression is associated with left-hemispheric changes in the frontal deep white matter and putamen.\(^16,17\)

### METHODS

#### Design and Sample

This study used a prospective cohort design. Subjects consisted of 115 depressed patients enrolled in the NIMH-sponsored Clinical Mental Health Clinical Research Center (MHCRC) at Duke University Medical Center. All subjects met DSM-IV criteria for major depression and were at least 60 years of age at baseline enrollment. Exclusion criteria for the MHCRC study include the following: another major psychiatric illness; alcohol or drug abuse or dependence; clinically diagnosed primary neurological illness, including dementia (see below); and medications, medical illness, or physical disability that affect cognitive function. After giving a complete description of the study to the subjects, we obtained written informed consent.

#### Assessment Procedures

At baseline, subjects received standardized clinical assessments, including the Hamilton Rating Scale for Depression (Ham-D),\(^18\) the Montgomery-Asberg Depression Rating Scale,\(^19\) and the Clinical Global Impression scale. A trained interviewer administered the Duke Depression Evaluation Schedule (DDES\(^20\)), which assesses depression by use of the NIMH Diagnostic Interview Schedule,\(^21\) as well as cognitive status, physical health, and social support. Clinical assessments were repeated every 3 months and when contact was clinically indicated. The DDES was repeated annually.

**Baseline cognitive screening.** Patients were excluded if they had dementia or suspected dementia at baseline. MHCRC geriatric psychiatrists clinically examined all subjects, reviewed medical records, interviewed family members, and conferred with referring physicians for all patients. At baseline, whereas most subjects (89.1%) had Mini-Mental State Exam (MMSE\(^22\)) scores above 24,
some severely depressed patients (10.9%) had scores below 25 (range: 18–24). MHCRC protocol is to follow such patients through an acute (8-week) phase of treatment to determine whether cognition improves. Subjects with a clinical diagnosis of dementia (DSM-IV) or whose MMSE scores remain below 25 are not followed longitudinally in the MHCRC. Thus, in the clinical judgement of the study geriatric psychiatrist and by established MHCRC protocol, dementia is effectively excluded at or close to baseline in all elderly depressed MHCRC subjects.

Baseline magnetic resonance imaging (MRI) procedure. All subjects were screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other condition where MRI was contraindicated. Subjects were imaged under an Institutional Review Board-approved protocol, with a 1.5-tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI), using the standard head (volumetric) radiofrequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the bridge of the nose, and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment.

High-resolution imaging for volume measurements. Two sets of dual-echo fast spin-echo (FSE) acquisitions were obtained, one in the axial plane for morphometry of most cerebral structures, and a second in a coronal oblique plane for segmentation of the hippocampus. The pulse sequence parameters were repetition time (TR) = 4,000 msec, and echo time (TE) = 30, 135 msec, with 32 KHz (±16KHz) full imaging bandwidth; echo train length = 16, a 256 × 256 matrix, 3-mm section thickness, 1 Nex and a 20-cm FOV (field of view). The images were acquired in two separate acquisitions, with a 3-mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first, so that the resulting data set consisted of contiguous sections. For the near coronal acquisition, the localizer scan was used to identify the anterior comissure–posterior commissure (AC–PC) line. Oblique, near-coronal images were prescribed perpendicular to this line, covering the entire brain from just anterior of the temporal lobe to a plane posterior to the lateral ventricles.

MR image-processing for brain volumes. Images were archived as normal procedure on magneto-optical disks in the MR Imaging Center. The MR images were then transferred to the Neuropsychiatric Imaging Research Laboratory (NIRL), located at Duke University Medical Center, for processing on SUN workstations, and secondary archive. Thin-slice, dual-echo FSE images, consisting of proton-density and T2-weighted images, were used for all processing. Hippocampal measurements used an oblique/coronal series of slices, and all other measures were done with axial images. Two computer programs were used to make volume measurements. Hippocampal volumes were determined with the GRID Program, which was developed at NIRL. All other volume measurements used an NIRL-modified version of MrX Software, which was created by GE Corporate Research and Development (Schenectady, NY) and originally modified by Brigham and Women’s Hospital (Boston, MA) for image segmentation.

MrX procedures for whole brain and cerebral hemispheres. The basic segmentation protocol used by NIRL was a modified version of that developed by Kikinis et al. and has been described previously. This was a supervised, semi-automated method that used the multiple MR contrasts available to identify different tissue classifications through a “seeding” process wherein a trained analyst manually selected pixels in each tissue type that was to be identified (such as gray matter, white matter, CSE, gray- and white-matter lesions, background). Once the brain was segmented into tissue types and the non-brain tissue stripped away through a masking procedure, specific regions of interest (ROI) were assessed by use of tracing and connectivity functions. The cerebral hemispheres were traced, and a mask was created and applied to the segmented brain. The final step was to run a summarizing program that calculated the volume of each tissue type within the specific ROI defined by the analyst. Volumes were determined for the whole brain and cerebral hemispheres.

GRID procedures for the hippocampus. The GRID Program was used to quantify the hippocampus. The GRID Program allows for semi-automated determination of ROI volumes and was based on a manual point-counting method. The program used a single MR contrast, creating a histogram of the image intensities. A 0.6-mm grid was then superimposed on the image, with the tissue type at each intersection pre-assigned by an
adjusted histogram. A combination of this tissue classification with manual tracing allowed for rapid determination of ROI volumes.

**Definition of the hippocampus.** On all slices, tracing began along the most inferior border of the main body of the hippocampus, then moved laterally along the border between the hippocampus and the inferior lateral ventricles. Along the medial and superior borders, tracing included any thin strips of white matter along the lateral or superior surface. Pockets of CSF were excluded; blood vessels were transected unless they were prominent or did not extend into the hippocampal body. If motion, poor contrast, or other factors rendered any one slice unreadable, a volume for that slice was generated by averaging the volumes from the previous and subsequent slices. If the first or last slices were unreadable, or if two middle slices were unreadable, the subject was excluded from analysis.

On each scan, tracing began with the most posterior coronal slice, then proceeded anteriorly. Measurement of the hippocampus began when the pulvinar nucleus of the thalamus obscured the crura fornicis; if the crus was only obscured on one side, then only that side was measured. On the first few slices, the lateral body of the hippocampus appears as a rough oval, which narrows medially into a thin strip of gray matter that curves downward along the border of the cistern. The fimbria, which extends from the superior surface of the hippocampus across the CSF into the white matter above, was transected at its narrowest point. Along the medial border of the hippocampus, the thin strip of gray matter was cut at its narrowest point, and tracing then continued around the hippocampal body to the starting point.

On more anterior slices, the amygdala begins to appear just superior to the hippocampus, which roughly resembles a kidney in shape, with no external connections. The amygdala–hippocampal transition zone appears as a diffuse area of gray matter between the anterior portion of the hippocampus and the posterior portion of the amygdala; as with the fimbria, this area was transected at its narrowest point, which was usually found between the inferior lateral ventricles and the cistern. Continuing anteriorly, the inferior lateral ventricles gradually shift from a vertical to a horizontal orientation, but remain superior to the hippocampus. The anterior border of the hippocampus was defined as the slice on which the inferior lateral ventricles appeared horizontally without any body of gray matter visible below them.

**Training and reliability.** All technicians received extensive training by experienced volumetric analysts. Reliability was established by repeated measurements on multiple MR scans before raters were approved to process study data. Also, an ongoing reliability study was conducted to ensure that the quality of volumetric analyses was maintained throughout the study. Intraclass correlation coefficients (ICCs) were as follows: total brain = 0.998; left cerebral hemisphere = 0.996; right cerebral hemisphere = 0.997; left hippocampus = 0.8; right hippocampus = 0.7.

**Determination of ApoE genotype.** After signing separate informed consent for genetic testing, 67 individuals underwent phlebotomy to collect a blood sample for ApoE genotyping. This component was added later to the MHCRC, so this smaller number reflects both new subjects and those whom we contacted after baseline assessment. White blood cells were processed, and ApoE genotypes were determined using a method previously described by Saunders et al.26

**Clinical follow-up.** The MHCRC operates in a naturalistic treatment milieu, using treatment guidelines established by the Duke Affective Disorders Program. Treatment modalities available include antidepressant medications, electroconvulsive therapy, and individual and group cognitive–behavioral psychotherapy. As indicated above, patients are evaluated when clinically indicated and at least every 3 months while they are in the study.

**Dementia diagnosis.** Patients are diagnosed with dementia in a three-step process: First, in all cases, the study geriatric psychiatrist assigns a diagnosis of dementia if the patient meets DSM-IV criteria for dementia. Second, as part of the MHCRC protocol, patients are administered annually a series of neuropsychological tests, including the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) battery,27 an instrument that is reliable, valid, and has shown usefulness in longitudinal studies with well-established normative standards.28 It is composed of tests of verbal fluency (animal generation), naming, praxis, and memory (word list learning test; word list, delayed recall; word list recognition; and delayed recall of the constructional praxis
The general screen is supplemented with other well accepted neuropsychological measures of higher-order cognition. For recent memory, the Logical Memory subtests from the Wechsler Memory Scale–Revised and the Benton Visual Retention Test are included. As a language-verbal retrieval screen, we used the Controlled Oral Word Association Test from the Multilingual Aphasia Examination; for attention, speed of processing, and conceptualization, the Trail-Making Tests Part A and B and the Symbol Digit Modalities Test. These tests were reviewed by the principal investigator (DCS) and the study’s neuropsychologist (KAW-B) to determine whether the subjects meet dementia criteria on the basis of testing. These results are then reviewed with the treating geriatric psychiatrist to achieve a consensus on diagnosis and date of conversion to dementia.

A third diagnostic avenue for some patients involves referral to the Duke Neurological Disorders Clinic to help clarify diagnosis in cases of early suspected dementia, mixed-etiologic dementia, or dementia with atypical presentations.

Specific dementia diagnosis, if available, and approximate date of onset of dementia are recorded. In many cases, patients present with cognitive decline in the context of cerebrovascular risk factors or severe subcortical white- and gray-matter vascular change; such patients, who represent the majority of dementia cases in our study, are labeled as dementia of undetermined etiology and consist of individuals with a clinical diagnosis of dementia possibly due to AD and/or cerebrovascular disease.

Data Analysis

Bivariate analyses of demographic, clinical, and imaging variables were performed on the non-dementia and dementia groups by use of chi-square analyses for categorical variables and t-tests for continuous variables. Volumes for the left and right hippocampus were analyzed separately as continuous variables. Also, in a manner similar to a previous report, left and right hippocampal volume was conceptualized as a dichotomous variable with subjects either being below or above the lowest quartile of volumes (roughly 2.67 ml on the left and 2.75 ml on the right). Survival analysis (Cox proportional-hazards [HR]), using the PHREG procedure (SAS Institute, Cary, NC) was performed on variables significant in bivariate models. Time-to-event for subjects who developed dementia was defined as the recorded date for conversion to dementia. Patients who did not develop dementia were right-censored for death, dropout from the study, or (for active study participants) if they did not show dementia at their last study visit. For each of these three possibilities, the appropriate date was recorded. Kaplan-Meier curves were generated using the SAS Lifetest procedure. To determine whether study subjects who withdrew differed from other subjects, we undertook a series of bivariate analyses comparing withdrawn and active subjects on baseline characteristics.

RESULTS

The 115 subjects ranged in age from 60 to 90 years (mean age: 70.2), 69.7% were female, and the group had a racial composition of 90.8% white and 9.2% black. Patients had length of follow-up between 64 and 1,848 days (median for the entire group: 681 days; median for non-dementia patients: 657 days).

Over the course of the study to date, 15 of 115 have developed dementia (13.0%). For the patients who developed dementia, duration of follow-up before dementia ranged from 320 to 1,267 days (median: 876). As far as types of dementia, five were categorized as AD, three with vascular dementia, and seven with mixed AD and vascular dementia.

As shown in Table 1, the dementia group, compared with the non-dementia group, was significantly older, had higher age at depression onset, and lower baseline MMSE score. They were marginally (p values between 0.1 and 0.2) more likely to be white, to have smaller cerebral volumes, and to be in the lowest quartile of left hippocampal volume. The two groups did not differ on gender, baseline Ham-D score, education, number of previous depression episodes, right quartile of hippocampal volume, mean left or right hippocampal volume, or ApoE genotype. There were only 67 subjects with ApoE genotype available, and significantly more dementia subjects than non-dementia had ApoE genotyping (84.2% vs. 52.0%; \chi^2 = 6.730; p = 0.009). When withdrawn subjects (n = 31, including 11 deaths) were compared with active subjects (n = 84), withdrawn subjects were older (p < 0.053), had lower baseline MMSE (p < 0.007), and had smaller total cerebral volumes (p < 0.018), but there were no differences be-
between the two groups on education, age at onset, or any of the hippocampal volume variables.

Variables significant in bivariate analyses (except age at onset, which was highly correlated with age) were included in survival analyses; namely, age, baseline MMSE score, the dichotomous left hippocampal volume variable, and total cerebral volume. As shown in Table 2, having left hippocampal volume in the lowest quartile at baseline was significantly associated with later emergence of dementia after covariates were controlled. Also, we examined survival, using the above variables along with ApoE genotype dichotomized as any ε4 allele vs. none. ApoE genotype did not contribute significantly to the model (HR = 1.523; 95% confidence interval [CI]: 0.469–4.945), and left hippocampal volume in the lowest quartile lost significance (HR = 2.140; CI: 0.700–6.543) in this smaller subsample. In a final model with only age and left hippocampal volume, small hippocampal volume remained significantly associated with dementia (HR = 2.663; CI: 1.034–6.859; p = 0.0424). Kaplan-Meier survival curves for the lowest quartile of left hippocampal volume for the dementia and non-dementia groups are shown in Figure 1.

Having small right hippocampal volume was not associated with later dementia in multivariate survival analysis controlling for age, baseline MMSE, and total cerebral volume (HR = 0.767; CI: 0.250–2.254; p = 0.643).

**CONCLUSIONS**

Our main finding that depressed non-dementia patients with small left hippocampal volumes at baseline were at a higher risk of emergence of later dementia provides further evidence linking geriatric depression, dementia, and the hippocampus. Previous cross-sectional studies examining the hippocampus in depression have yielded conflicting results, with some finding a difference in hippocampal volume between depressed patients and control subjects, whereas others have not. We also found considerable variability in hippocampal volume in geriatric depression. This longitudinal study of geriatric depression thus extends previous work to find that later dementia may be a consequence of small hippocampal volume in elderly depressed patients.

An alternate interpretation for our findings in that small left hippocampal size on neuroimaging may be a marker for dementia in evolution in depressed patients.

### TABLE 1. Baseline characteristics of later depressed subjects with and without dementia

<table>
<thead>
<tr>
<th></th>
<th>Entire sample</th>
<th>No dementia</th>
<th>Dementia</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 115)</td>
<td>(n = 100)</td>
<td>(n = 15)</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean (se)</td>
<td>70.16 (0.68)</td>
<td>68.79 (6.90)</td>
<td>78.67 (0.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, female, n (%)</td>
<td>81 (70.43)</td>
<td>69 (69.0)</td>
<td>12 (80.0)</td>
<td>0.384</td>
</tr>
<tr>
<td>Race, white, n (%)</td>
<td>104 (90.43)</td>
<td>92 (92.0)</td>
<td>12 (80.0)</td>
<td>0.141</td>
</tr>
<tr>
<td>Education, years, mean ± SD</td>
<td>13.23 ± 0.30</td>
<td>13.25 ± 0.31</td>
<td>12.92 ± 1.13</td>
<td>0.732</td>
</tr>
<tr>
<td>Baseline Ham-D score, mean ± SD</td>
<td>22.09 ± 0.72</td>
<td>21.97 ± 0.77</td>
<td>22.93 ± 2.38</td>
<td>0.659</td>
</tr>
<tr>
<td>Age at depression onset, years, mean ± SD</td>
<td>44.57 ± 1.97</td>
<td>43.06 ± 2.00</td>
<td>58.27 ± 6.40</td>
<td>0.016</td>
</tr>
<tr>
<td>n previous episodes, mean ± SD</td>
<td>3.28 ± 0.44</td>
<td>3.50 ± 0.50</td>
<td>2.67 ± 0.98</td>
<td>0.535</td>
</tr>
<tr>
<td>Baseline MMSE, mean ± SD</td>
<td>27.69 ± 0.23</td>
<td>27.98 ± 0.22</td>
<td>25.93 ± 0.94</td>
<td>0.028</td>
</tr>
<tr>
<td>Apolipoprotein genotype, n with any ε4 allele (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (23.88)</td>
<td>12 (21.82)</td>
<td>4 (33.33)</td>
<td>0.397</td>
</tr>
<tr>
<td>Left hippocampal volume, ml, mean ± SD</td>
<td>2.92 ± 0.03</td>
<td>2.93 ± 0.04</td>
<td>2.86 ± 0.13</td>
<td>0.472</td>
</tr>
<tr>
<td>Right hippocampal volume, ml, mean ± SD</td>
<td>3.03 ± 0.04</td>
<td>3.03 ± 0.04</td>
<td>2.96 ± 0.12</td>
<td>0.516</td>
</tr>
<tr>
<td>Left hippocampal volume, n in lowest quartile (%)</td>
<td>28 (24.35)</td>
<td>22 (22.0)</td>
<td>6 (40.00)</td>
<td>0.130</td>
</tr>
<tr>
<td>Right hippocampal volume, n in lowest quartile (%)</td>
<td>29 (25.22)</td>
<td>24 (24.0)</td>
<td>5 (33.33)</td>
<td>0.438</td>
</tr>
<tr>
<td>Total cerebral volume, ml, mean ± SD</td>
<td>1,137.06 ± 12.86</td>
<td>1,143.46 ± 14.38</td>
<td>1,093.80 ± 29.12</td>
<td>0.193</td>
</tr>
<tr>
<td>Time in follow-up, days, mean ± SD</td>
<td>831.57 ± 500.20</td>
<td>831.50 ± 511.85</td>
<td>851.94 ± 441.65</td>
<td>0.997</td>
</tr>
</tbody>
</table>

**Note:** se = standard error of the mean; Ham-D = Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Exam; SD = standard deviation.

<sup>a</sup> Values given are for t-tests for continuous variables, and χ² for categorical variables.

<sup>b</sup> Apolipoprotein-E genotyping was available on 67 subjects, 55 without and 12 with dementia.

<sup>c</sup> Kruskal-Wallis test.
who have not yet met criteria for a clinical diagnosis of a dementing disorder. Our relatively short length of time for follow-up is consistent with the notion that for some individuals, the occurrence of depression in late life may be the heralding symptom of a dementing process. Small hippocampal volume has been shown in populations at risk for AD, such as those with mild cognitive impairment, both at baseline and with longitudinal neuroimaging. Our method of excluding individuals who did not meet clinical criteria for dementia would not exclude those subjects with a neurodegenerative process that had not become manifest. Yet, clinically, many of these depressed patients did well for several years before exhibiting cognitive decline. Another explanation is that some individuals may have had smaller hippocampi over a much longer period of time (perhaps congenitally), a condition that may have predisposed them to developing depressions first and dementia later. Further studies are clearly needed to determine whether course of depression and treatment affect the risk or age at onset of dementia.

Our finding was significant for the left hippocampus, but not the right. The issue of laterality is interesting and was noted in previous studies, with hippocampal volume found to be smaller among depressed patients compared with control subjects only on the left side. It is unclear why left but not right hippocampal volume should be significant. One study found a nonsignificant trend for an association between smaller right hippocampal volume and later dementia, so insufficient sample size in our study may in part explain the lateralizing findings. However, other studies of post-stroke depression in geriatric depression have noted left-sided findings. It is not known whether hippocampal atrophy in geriatric depression is a direct consequence of vascular change. With the interconnectedness of the hippocampus and other brain regions, it may be that vascular disruption of frontal deep white matter and basal ganglia structures adversely affects hippocampal function, resulting in the neuronal cell loss and decreased volume seen on MRI. Further studies are required to understand the mechanisms leading to decreased hippocampal volume in geriatric depression.

Absence of a finding on the right may also be a product of the tests we use to define dementia. Small left hippocampal volume is likely to correlate with impairment on conventional verbal memory tests used in the diagnosis—and definition—of dementia. Spatial memory tests are more likely to be affected by changes in the right hippocampus, and they are less likely to be considered in the diagnosis of dementia. In future studies, we plan to examine data from our neuropsychological test battery to better understand the relationship between cognitive performance, hippocampal volume, and the later emergence of a dementia syndrome in geriatric depression.

Another potential reason why we failed to find a significant association on the right is that our method may have introduced excessive variability. The ICC for the left hippocampal was 0.8, but it was only 0.7 on the right.

Our finding of smaller left hippocampal volume predicting later dementia is at variance with a previous study of Swann et al. that found that hippocampal atrophy among AD patients did not predict cognitive decline. That study followed five dementia patients and five age-matched control subjects over 2 years. Our study examined older depressed patients, and none of the depressed subjects showed dementia at baseline, so the two studies may not be directly comparable.

The relationship between hippocampal volume, ApoE genotype, and dementia is complex, with reports finding greater hippocampal volume loss over time in ApoE e4 individuals compared with non-e4 individuals, in both dementia and non-dementia populations. In our survival analysis, we examined these variables in a

### TABLE 2. Survival analysis for left hippocampal volume (lowest quartile) in 97 subjects (14 with dementia)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>p</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.1052</td>
<td>0.0419</td>
<td>6.29101</td>
<td>0.0121</td>
<td>1.111</td>
<td>1.023–1.206</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>-0.1096</td>
<td>0.1040</td>
<td>1.11092</td>
<td>0.2919</td>
<td>0.896</td>
<td>0.731–1.099</td>
</tr>
<tr>
<td>Total cerebral volume</td>
<td>0.0016</td>
<td>0.0023</td>
<td>0.48300</td>
<td>0.4871</td>
<td>1.002</td>
<td>0.997–1.006</td>
</tr>
<tr>
<td>Small left hippocampal volume</td>
<td>1.0158</td>
<td>0.4913</td>
<td>4.27443</td>
<td>0.0387</td>
<td>2.762</td>
<td>1.054–7.234</td>
</tr>
</tbody>
</table>

Model: $-2 \log L \chi^2 = 23.060, 4 \text{ df (p = 0.0001)}$. 
Note: df = 1 for these variables; MMSE = Mini-Mental State Exam.
subset of patients with ApoE genotyping. Hippocampal volume lost significance in the model, a finding that may be a function of the smaller sample size, but also may be an indication that hippocampal volume is influenced by ApoE genotype.

Some potential limitations to our study warrant discussion. First, our method of assessing dementia at baseline may not have excluded early cases of dementia. Both subclinical and early dementia are difficult to diagnose, and our reliance primarily on clinical diagnosis may have allowed a few such patients into the study. We chose not to rely on an arbitrary measure, such as a cutoff score on the MMSE, because this method is not perfectly sensitive or specific. Moreover, many depressed patients with lower MMSE scores do experience significant cognitive improvement with acute treatment. Our method of following such patients in the acute phase to track improvement in cognitive status was implemented to include such patients and to minimize the likelihood of including patients with suspected dementia.

The use of a 3-mm slice thickness for the MRI scans may not allow optimal definition of hippocampal boundaries. This method was designed when the study started in 1994, but is no longer state-of-the-art. The longitudinal nature of the study precluded any change in the imaging protocol so that slice thickness did not vary between patients.

Another concern may be the number of variables used in the survival analytic models versus the relatively small number of events. To limit over-fitting the model with excessive independent variables, we developed a parsimonious model containing only significant variables—age and hippocampal volume—and found that both remained highly associated with later dementia. The relatively small numbers of dementia subjects also prevented us from undertaking separate analyses of hippocampal volume by type of dementia.

Given that this is a study of depressed individuals, with no comparitor group of non-depressed control subjects, we cannot draw conclusions about the role of hippocampal volume in geriatric depression per se. Caution is also warranted about making broad statements about the relationship of depression to dementia. In data not shown, we did examine hippocampal volumes in a sample of 66 elderly nondepressed control subjects and found that mean left and right hippocampal volumes were 2.97 and 3.09 ml, respectively, and that the cutoffs for the lowest quartile of left and right hippocampal volume were at 2.70 and 2.76 ml, respectively. These values are only slightly greater than those in the non-dementia depressed sample.

The finding that depressed patients with small left hippocampal volumes may be at risk for later emergence of dementia symptoms may have implications for both basic and clinical research. Neuroscience studies directed at understanding how biological processes involved in hippocampal change are related to expression of affective illness should inform our understanding of both geriatric depression and dementia. The finding that one may predict later decline in cognition and development of dementia using hippocampal volume may lead clinicians to add agents that enhance cognition or delay onset of dementia to an antidepressant regimen in vulnerable patients. The question remains as to how directly accessible the finding is for practicing clinicians. Our method used a computer-generated summation of two-dimensional slices to determine hippocampal volume. Research is needed to examine the predictive ability of more simple measures, for example, measurements of hippocampal width on two-dimensional scans. Such studies would put such information in the hands of neuroradiologists and geriatric psychiatrists who are involved in formulating clinical decisions. Finally, studies of longitudinal changes in hippocampal volume are needed in order to correlate

---

**FIGURE 1.** Kaplan-Meier curves for left hippocampal volumes (above and below lowest quartiles)

![Kaplan-Meier curves for left hippocampal volumes](image)

*Note: A = curve for those above lowest quartile; B = curve for those below lowest quartile.*
progression of atrophy with cognitive change and the emergence of dementia.

Dr. Steffens thanks Drs. Carl F. Pieper, Hayden B. Bosworth, and P. Murali Doraiswamy, members of his Masters of Health Science in Clinical Research Examining Committee, for their review of the manuscript and helpful comments. The authors also thank Dr. Douglas Marchuk and Ms. Ingrid Stensson, in the Department of Human Genetics, Duke University Medical Center for processing of DNA and determination of ApoE genotype. Ms. Denise Fetzer, in the Neuropsychiatric Imaging Research Laboratory, for her expert technical assistance for the MRI volumetric analysis, and Mr. Tim Blitchington, in the NIRL, for development of the GRID program.

This work was supported by grants P30 MH40159, R01 MH54846 and K07 MH01367 from NIMH.

References

unipolar major depression: a magnetic resonance imaging study. Biol Psychiatry 2000; 47:1087–1090