MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease

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Article abstract—We evaluated a new magnetic resonance (MR)-based technique for performing volumetric measurements of temporal lobe structures. The technique was designed to assist in making the clinical diagnosis of dementia of the Alzheimer type (DAT). We chose specific anatomic regions of interest because of their known involvement in memory function and in the neuropathology of DAT and used a regression model to assess the effects of age on the volumes of the anterior temporal lobe (ATL) and the hippocampal formation (HF). These measurements were normalized by total intracranial volume (TIV). The volumetric measurements of both the normalized ATL and HF were significantly smaller ($p < 0.001$) in DAT patients (N = 20) than in controls (N = 22), but the HF volumes provided much better separation between the two groups. Eighty-five percent of the DAT patients fell below the range of the HF/TIV measurement for the control subjects. This separation held up over the entire age range studied. Normalized volumes of both the HF and ATL decreased with age significantly for both the DAT patients and the controls. These results support the contention that MR-based HF volumetric measurements are accurate in differentiating DAT patients from cognitively normal elderly individuals. This technique may be a useful adjunct in making the clinical diagnosis of DAT.

NEUROLOGY 1992;42:183-188

While the accuracy of making the clinical diagnosis of dementia of the Alzheimer type (DAT) is reasonably high (70% to 90%), difficulties remain in differentiating early DAT from the cognitive changes found in normal aging.[1-7] Criteria for the clinical diagnosis of dementia have been proposed by the DSM-III-R and a National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) task force; however, in the absence of a biologic marker, the definitive diagnosis can be made only with a biopsy or at autopsy.[1,2] The clinical diagnosis is most difficult in the older age groups, and assessing the significance of memory changes in this age group can be particularly challenging.

We are proposing the use of a recently developed magnetic resonance (MR) imaging technique for the volumetric measurement of the anterior temporal lobe (ATL) and hippocampal formation (HF) to aid in the clinical diagnosis of DAT.[8-12] The rationale for using this technique in the diagnosis of DAT is as follows: (1) a brain imaging study is recommended as part of the evaluation of patients with dementia;[1-7] (2) MR is superior to CT in accurately imaging the temporal lobe and limbic structures involved in memory;[8-13] (3) a memory impairment is often the earliest and most severe clinical manifestation in patients with DAT;[3-7] (4) temporal lobe limbic structures, in particular the HF, are intimately involved in the aspect of memory function that fails in DAT;[1-7] and (5) these limbic system structures are extensively involved histopathologically in DAT.[14-20]

We developed the proposed MR-based volumetric technique and have found it to be reproducible and valid in several clinical and research settings.[8-12] The reliability of the technique has been documented by repeated measures testing, and the reproducibility of the results has been excellent.[8] The accuracy of the volumetric measurements has been demonstrated by correlations with phantoms of known volume.[8] The technique has been used to measure the HF volumes of patients being evaluated for surgery for medically intractable epilepsy, and an excellent correspondence has been found between the atrophic HF, as assessed by MR, and the site of the active epileptogenic focus.[10] Finally, a study correlating MR volumes of the HF with the degree of mesial sclerosis found in surgical speci-

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Supported in part by grants from the National Institute on Aging: AG06786, Mayo Clinic Alzheimer's Disease Patient Registry, and AG08031-01-CA, Mayo Clinic Alzheimer's Disease Core Center; and the Mayo Foundation.

Received April 2, 1991. Accepted for publication in final form July 2, 1991.

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mens from epilepsy patients demonstrated excellent agreement between the atrophy seen on MR and neuronal loss in the HF.[12]

The specific purpose of this project was to determine whether MR-based volumetric measurements of the HF and ATL could discriminate between patients with probable DAT and cognitively normal elderly individuals.

Methods. *Patients.* This study included 20 patients with probable DAT and 22 healthy, cognitively normal individuals of similar age. Most of the DAT patients and all the controls were drawn from the Mayo Clinic Alzheimer's Disease Patient Registry. Additional DAT patients were recruited from the referral practice of a neurologist (R.C.P.), and these patients received essentially the same evaluation as patients drawn from the Alzheimer's Disease Patient Registry.

Patients and controls were recruited into the Mayo Clinic Alzheimer's Disease Patient Registry from individuals coming to the Division of Community Internal Medicine at the Mayo Clinic for their annual general medical examinations. As part of the Alzheimer's Disease Patient Registry, all patients and controls received medical and neurologic examinations performed by an internist and neurologist, respectively. A complete history was taken from the patient and another knowledgeable source. Laboratory studies were performed, including a complete blood count, chemistry profile, RPR, thyroid function studies, B_{12}, folic acid, chest x-ray, and an ECG. All patients and controls underwent neuropsychological tests, including the Wechsler Adult Intelligence Scale-Revised, the Wechsler Memory Scale or the Wechsler Memory Scale-Revised, the Rey Auditory Verbal Learning Test, the Short Test of Mental Status, the Hachinski Ischemic Index, the Geriatric Depression Scale, and the Global Deterioration Scale, under the supervision of a neuropsychologist.[21-24] All of the DAT patients met the criteria for probable DAT as outlined by the NINCDS/ADRDA task force.[1] The DAT patients were in the mild to moderate stages of the disease and received a Global Deterioration Scale rating of 3 or four.[25]

The 22 control subjects had an evaluation identical to that of the probable DAT patients. They had no cognitive complaints and were judged to be cognitively normal and functioning independently by the Alzheimer's Disease Patient Registry Consensus Committee comprised of an internist, two neurologists, two neuropsychologists, and three nurses involved in the evaluation of these patients. One of us (R.C.P.) asked the patients for their willingness to participate in this MR study. The risks and benefits of participation in this project were discussed with the patients, and no compensation was provided. All of the control subjects had a Global Deterioration Scale rating of 1, which was normal. None of the patients or controls were judged to be depressed, and all had Hachinski Ischemic scores of less than four. None of the patients or controls had clinical evidence for strokes nor did they have any cortical infarctions on the T_2-weighted MR images.

MR image acquisition. All studies were performed at 1.5 T (GE Signa, Milwaukee, WI). After scout sequence(s) to insure symmetric positioning of the patient's head, sagittal images were obtained with the following parameters: 5-mm sections, 24-cm field of view (FOV), 500/20/2 (TR/TE excitations), 192 phase encoding steps. The plane of the left HF was located from the sagittal images, and the next (oblique coronal) imaging sequence was acquired perpendicular to this plane with the following parameters: 24-cm FOV, 500/20/2, 256 phase encoding steps, 4-mm slice thickness interleaved (with no interslice gap). The following three features, which are necessary for accurate volumetric measurements, were incorporated into the design of this pulse sequence: (1) the sequence was tailored to be perpendicular to the long axis of the HF in each individual; (2) it was T_1-weighted, thereby providing high brain-CSF and gray-white matter contrast; and (3) individual image slices were thin and contiguous, which minimized partial volume averaging, thereby enhancing the accuracy of volume measurements. Both temporal lobe structures (ATL and HF) were measured from this oblique coronal pulse sequence.

All subjects also underwent an axial double spin echo sequence. This sequence was used to exclude subjects with possible cortical infarctions but was not used for volumetry.

Image processing: volume measurements. The volume measurement technique has been described in greater detail elsewhere.[8-11] Briefly, image processing was done with ANALYZE software (Biodynamics Research Unit, Mayo Foundation, Rochester, MN) running on an independent Sun 3/160 c workstation.[26] The software employs a semiautomated technique that combines tracing and thresholding. High-contrast region of interest boundaries, which were formed by a brain-CSF interface, were defined by a gray scale threshold, which was set halfway between background and brain intensity. Region of interest boundaries which were not defined by high gray scale contrast were manually traced with a mouse-driven cursor. Gray scale values of pixels external to the outline were set to zero. Once the boundary of the region of interest had been defined on serial planimetric sections, its volume in voxels was determined automatically by counting the number of pixels within the threshold range.

Boundary definitions for the temporal lobe structures have been published.[8-11] The posterior boundary for both the ATL and HF was defined by the oblique coronal plane which intersected the posterior commissure on the cross-referenced midline sagittal image. In-plane circumferential ATL and HF boundaries are defined in figures 1 and 2, respectively. The HF was defined to include the subiculum, Ammon's horn (CA1-CA4), dentate gyrus, and associated white matter tracts (alveus, fimbria); Ammon's horn within the posterior uncus was included in the HF region of interest boundary. Definition of these HF margins on the workstation screen was guided by continually referencing a detailed neuropathologic anatomic atlas.[27] Disarticulation of the HF head from the amygdala and uncinate gyrus on the most anterior sections was aided by recognizing the undulating contour of the pes digitations (figure 2) and also by the fact that the alveus provides a high signal intensity (white matter) marker defining the superior border of the head of the HF where it directly abuts the overlying amygdala.

Total intracranial volume was measured on the sagittal images by tracing the contour of the inner table. Both regions of interest (HF and ATL) were normalized for intersubject variation in head size by dividing by the total intracranial volume (TIV) in each case. Precedent for this "ratio" approach to region of interest normalization comes from both the CT literature[28-31] and the population-based autopsy studies of brain weight.[32-34] These normalized indices (HF/TIV, ATL/TIV) are ratios that

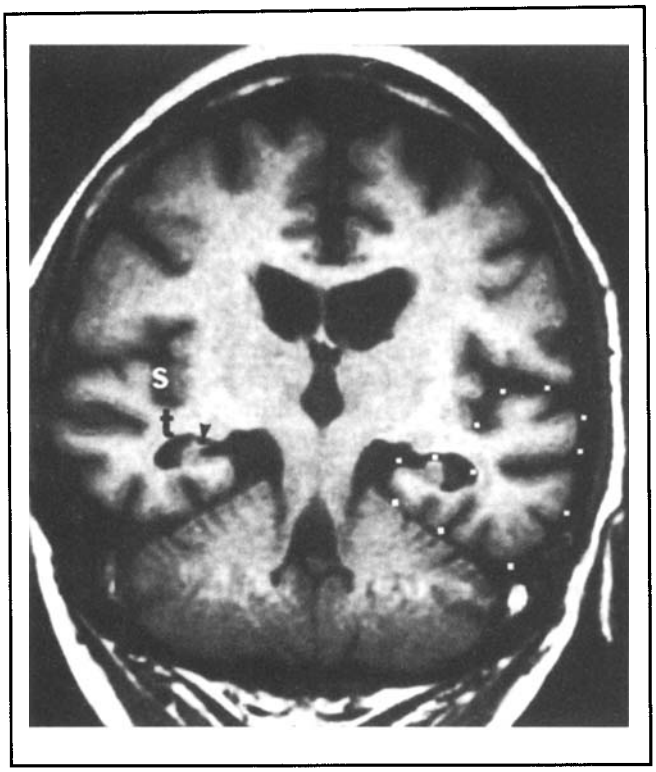

Figure 1. In-plane circumferential ATL boundaries. Oblique coronal image. ATL boundaries outlined by squares on the left. Proceeding clockwise on the left side, boundaries are formed by the choroid fissure, a vertical manually drawn line through the temporal stem, sylvian fissure, and subarachnoid space surrounding the lateral, basal, and medial temporal gyri. S = vertical portion of sylvian fissure, t = temporal stem, arrowhead = choroid fissure. Left is on the reader's right in figures 1 to 3.

express the region of interest (HF or ATL) as a percentage of TIV.

Volume measurements were performed in an unbiased manner by a neuroradiologist (C.R.J.) with extensive experience as an ANALYZE software operator. A trained study assistant loaded the control and patient MR imaging studies randomly into workstation memory. Each case was identified by a number only. Measurements of five to 10 subjects were made per session. The operator making the measurements (C.R.J.) was blinded to the clinical diagnosis, age, and sex in each case, which eliminated any potential measurement bias in the volumetric data.

Results. The demographic and volumetric data are summarized in the table. The two clinical groups are closely matched in age and gender distribution. Symbols for individual temporal lobe regions of interest in the table represent the sum of the right plus the left side; for example, the symbol HF represents the right plus left HF volume in cm^3. Both the mean normalized HF and ATL were smaller in DAT patients than controls (figure 3), despite the fact that the patients were slightly younger on average than controls. There was no difference in the normalized volumes for men and women on either measure ($p > 0.05$). Temporal lobe regions of interest for men and women could therefore be

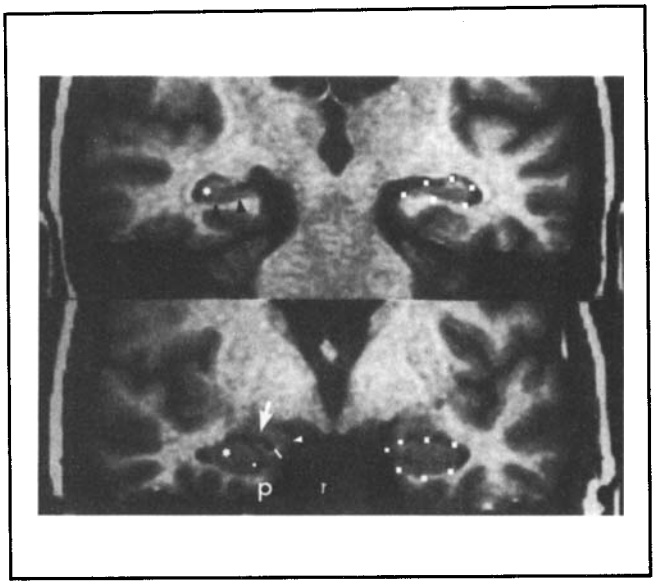

*Figure 2. In-plane circumferential HF boundaries. Oblique coronal images. (•) = hippocampal fissure, p = parahippocampal gyrus, * = Ammon's horn (CA1 subfield area), black arrowheads = subiculum, arrow = amygdala (cortical nucleus and accessary basal nucleus), and white arrowhead = uncinate gyrus. Top figure is an image through the posterior HF body. Bottom figure is the most anterior HF section through the head (pes hippocampus). HF boundaries are outlined on the left by squares. Proceeding clockwise on the left side, HF boundaries are formed by the uncal cistern, choroid fissure (CSF space above the pes digitations on the anterior HF section at bottom), temporal horn, and the gray-white interface formed by the subiculum and underlying parahippocampal gyrus white matter. Note the undulating superior border of the HF head (the pes digitations) which distinguishes it from the overlying amygdala. The dash (—) on the right indicates the boundary we use to separate the HF head from the uncinate gyrus; we follow criteria outlined in the neuroanatomy text by Duvernoy.[27]*

analyzed together without treating gender as a covariate. The mean TIV of patients and controls was essentially the same ($p > 0.05$). ATL volumes are reported with the HF volume included. ATL volume is typically an order of magnitude greater than that of the HF. Analyses done both ways demonstrated that subtracting the HF from ATL volumes had no effect on the intergroup ATL volumetric differences.

Figures 4 and 5 represent scatter plots and linear regression of normalized volumes on age for DAT patients and control subjects (HF/TIV, figure 4; ATL/TIV, figure 5). The normalized ATL and HF both decrease with age for DAT patients and controls. An analysis of covariance of normalized volume on age demonstrated that the volumes of ATL ($p < 0.001$) and HF ($p < 0.001$) were significantly smaller for the DAT patients than for the controls. Inspection of figures 4 and 5 indicates that the HF/TIV measurement was more effective at separating the two groups. Figure 4 (HF/TIV) shows that only three of the 20 DAT patients fell within

the range of the controls; 85% of the DAT patients fell below the range of control subjects.

The slope of the regression lines is not different between patients and controls for the ATL/TIV but is significantly different for the HF/TIV ($p = 0.025$). The HF/TIV decreases more rapidly with age for DAT patients than controls, and in this study, separation of controls from patients was more complete in older subjects.

Discussion. The data from this study demonstrate that this MR technique may be useful in distinguishing patients with probable DAT from age-matched controls. Volumetric measurement of the HF separated the patients with DAT from the normal controls reasonably well. Only three of the patients overlapped, and consequently, this measurement technique is more promising than other quantitative imaging techniques previously available.[28-31] While the volumetric measurements of the ATL also separate the two groups in a significant fashion, there is sufficient overlap between the two groups to make this measure less useful. Consequently, we recommend the use of the HF measure to assist in the diagnosis of DAT.

We also found increasing volume loss with age in controls for both normalized temporal lobe regions of interest (HF/TIV and ATL/TIV). This is consistent with the age-related atrophy that occurs in both CT-based[28-31] and pathologic[32-36] brain quantitation studies. The slopes of the normalized volumes when regressed on age did not differ between the DAT patients and the controls for the normalized ATL measure but did differ significantly for the normalized HF measure. The significance of this finding is uncertain at this time, and we will acquire additional data for further amplification.

A question can be raised concerning the validity of using the clinical diagnosis of DAT as the criterion against which to assess the volumetric measures. Since the inception of the Mayo Clinic Alzheimer's Disease Patient Registry, autopsies have been obtained on 18 patients and controls. All of the cases with the diagnosis of probable DAT have been correctly classified thus far when the clinical and neuropathologic diagnoses have been compared. Therefore, it appears that, while the clinical diagnosis of DAT is not the ideal gold standard, there is at least good agreement with the ultimate neuropathologic diagnosis obtained at autopsy in the registry from which subjects for this study were drawn.

For nearly two decades, investigators using CT have attempted to quantify hemispheric cerebral atrophy in order to differentiate patients with DAT from cognitively normal elderly individuals.[28-31] Semiautomated CT-based measurement techniques suffer from several inherent technical limitations when compared with MR. CT-based techniques have been hampered by a lack of specificity in separating individual patients with DAT from normal elderly persons,[28-31] and this is the primary reason

Table. Demographic data and temporal lobe volumetric measurements in DAT and controls

	DAT	Controls
No.	20	22
Age (yrs)	73.45 ± 10.6	76.3 ± 11.3
Education (yrs)	15.0 ± 3.7	13.4 ± 3.4
M/F	7/13	10/12
STMS	22.39 ± 7.3	33.67 ± 2.1
VIQ	88.47 ± 14.7	105.46 ± 9.9
PIQ	78.71 ± 12.3	104.76 ± 14.1
FSIQ	84.50 ± 12.8	106.00 ± 11.6
TIV (cm^3)	1,454.4 ± 152.1	1,435.0 ± 146.1
HF/TIV	2.0 ± 0.05	2.8 ± 0.03
ATL/TIV	6.6 ± 0.6	7.3 ± 0.7

STMS Short test of mental status. Range 0-38 with cut-off between normal and dementia at 29.[25]
VIQ Verbal IQ.
PIQ Performance IQ.
FSIQ Full scale IQ.
TIV Total intracranial volume.
HF/TIV Ratio of right plus left hippocampal formation divided by total intracranial volume ($\times 10^3$).
ATL/TIV Ratio of right plus left anterior temporal lobe divided by total intracranial volume ($\times 10^2$).

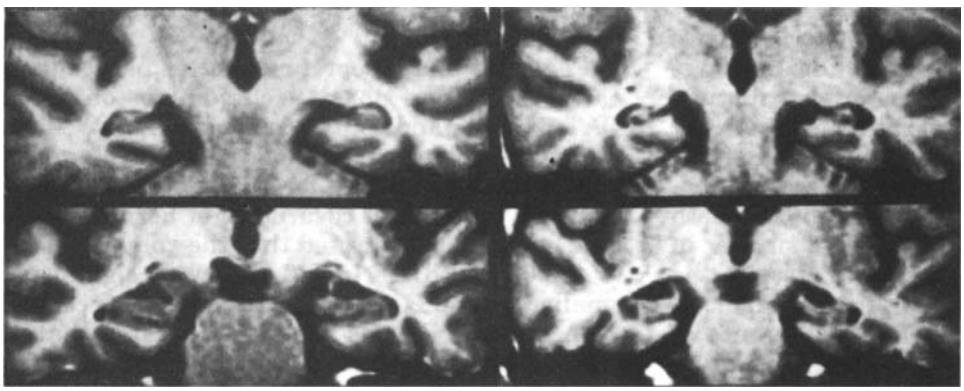

Figure 3. HF comparison: control versus DAT. Images on the left are at the level of the hippocampal body (top) and head (bottom) of a 79-year-old female control subject. Images on the right are through similar anatomic levels of a 77-year-old woman with DAT. Note the atrophy of the HF (with lesser atrophy of the temporal lobe) in the DAT patient compared with the control.

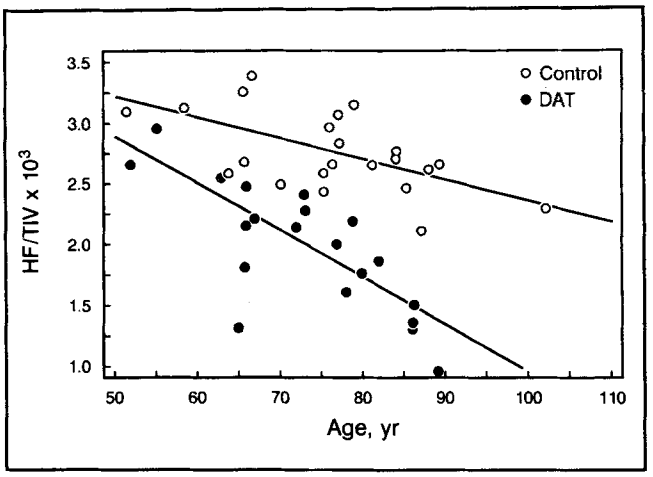

Figure 4. Hippocampal formation volumetry. Scatter plot and linear regression of normalized HF (HF / TIV × 10^3) on age for control and DAT subjects.

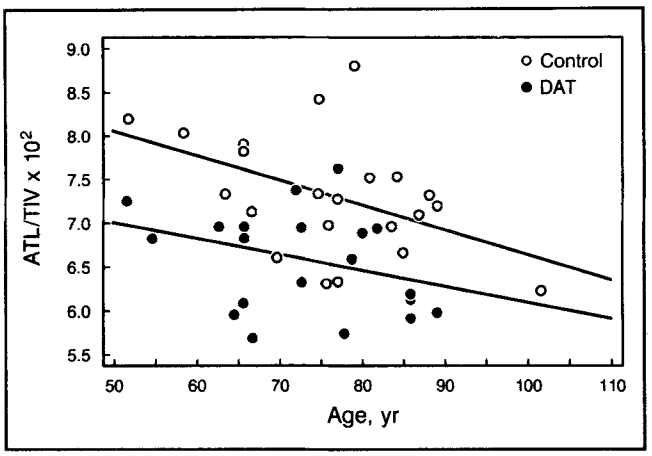

Figure 5. Anterior temporal lobe volumetry. Scatter plot and linear regression of normalized ATL (ATL / TIV × 10^2) on age for control and DAT subjects.

that CT-based quantitation of atrophy has not gained widespread clinical acceptance.[3,4] It is plausible that the most significant limitation in previous semiautomated CT-based attempts to quantify global cerebral atrophy in DAT was that the areas of the brain that are most severely involved (the temporal lobe, particularly the HF) were not included in the regions of interest. Indeed, several recent nonvolumetric CT studies[37-40] in which the CSF spaces in the anterior temporal region were perceptually evaluated have claimed impressive accuracy in separating patients with DAT from elderly controls. More recently, semiautomated MR-based whole-brain and lobar volumetric approaches have been described.[41,42]

While this manuscript was in preparation, a paper was published by Kesslak et al[43] on the same topic. Kesslak et al use an MR-based volumetric technique that seems similar to the one we have previously published,[8-11] although some technical details were not fully described. They measured volumes of the HF and parahippocampal gyri in patients with probable DAT (N = 8) and elderly controls (N = 7). In an earlier study, Seab et al[44] used MR-based single-slice (planimetric) measurements of the HF to separate DAT patients (N = 10) from elderly controls (N = 7). In both of these studies, the probable DAT and control groups were completely separated by quantitative measures, ie, no overlap was found. Conversely, in our study with a larger sample size (roughly three times larger than that of Kesslak et al), DAT patients were incompletely separated from controls on the basis of HF volume measurements. We feel that while hippocampal volumetry is useful, it will not provide an absolute diagnostic standard when applied prospectively to the population at risk for DAT.

In summary, our technique of MR-based HF volumetric measurements shows promise in providing useful diagnostic information for separating patients with probable DAT from normal elderly subjects. This technique may prove to be a clinically useful adjunctive test in elderly patients suspected of having DAT. This can be considered a cost-effective approach because patients evaluated for dementia must undergo a cross-sectional imaging study to exclude other treatable causes of dementia. Simple visual inspection of the MR images for atrophy may not be adequate, because the model we described incorporates an adjustment for both age and total intracranial volume. Ultimately, it will be important to expand this database to develop age-specific sensitivity and specificity figures. In addition, the technique will be applied to patients with early memory deficits in the absence of a more generalized cognitive decline to determine if this technique will be able to predict which patients will ultimately develop dementia.

Acknowledgments

Ms. Ellen Ptacek and Mrs. Brenda Maxwell for their typing.

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