Cinguloparietal Atrophy Distinguishes Alzheimer Disease From Semantic Dementia

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Background: Progressive brain atrophy is associated with Alzheimer disease (AD) and other dementias. Regional differences in brain atrophy may reflect clinical features of disease.

Objective: To identify regions of cerebral atrophy that are associated with AD vs other dementias.

Setting: University hospital dementia clinic.

Participants: Eleven patients with AD and 11 with semantic dementia (SD), matched for age, sex, education, and degree of overall cognitive impairment and 15 normal controls.

Methods: Voxel-based morphometry was used to compare patterns of gray matter loss, measured on T1-weighted magnetic resonance images, between patients with AD or SD, a subtype of frontotemporal lobar degeneration, and controls. Statistically significant differences in regional gray matter concentration, after multiple-comparisons correction, between groups of subjects were identified.

Results: Patients with AD were more impaired than those with SD on tests of visuospatial function and on simple calculations. Consistent with these neuropsychological deficits, the most significant area of atrophy in the AD group was the left parietal cortex vs controls ($z=5.0; P=.04$). Compared with SD, AD was associated with more atrophy in the left parietal lobe ($z=5.6; P=.04$) and bilaterally in the posterior cingulate/precuneus ($z=5.1; P=.04$). A discriminant function analysis demonstrated that the degree of atrophy of right posterior cingulate, left parietal lobe, right amygdala, and right anterior temporal lobe structures correctly classified 96% of the patients.

Conclusion: Alzheimer disease is associated with a specific pattern of cortical atrophy compared with SD.

Arch Neurol. 2003;60:949-956

NEW TREATMENTS for Alzheimer disease (AD) have been designed to target specific components of the AD neurodegenerative mechanism and are thus unlikely to be useful in other forms of dementia. For this reason, it will be important to distinguish other common causes of dementia, including vascular disease, Lewy body disease, and Pick complex disorders, from AD at early stages of the disease, when strategies to decrease brain β-amyloid levels will have the largest potential benefit. Neuroimaging is a useful tool in the diagnosis of dementia.1 Fluorodeoxyglucose positron emission tomography of AD shows early parietal and cingulate hypometabolism, which is predictive of progression to dementia2 and is specific to AD.3

In contrast, most structural analyses of AD have focused on atrophy of medial temporal lobe structures as measured on high-resolution T1-weighted magnetic resonance images (MRIs).4,5 Hippocampal and entorhinal cortex volumes reflect disease severity in AD6,7 and are correlated with neuropsychological measures of memory function in AD.8,9 Moreover, the rate of hippocampal volume loss predicts which patients with mild cognitive impairment will go on to develop AD.10 Atrophy of extratemporal limbic structures is also predictive of a diagnosis of AD11,12; however, few structural studies have measured the parietal lobe structures that were abnormal by positron emission tomography. To best identify clinically relevant regions of brain atrophy, an open-ended, systematic method of analysis of brain atrophy is necessary.

Voxel-based morphometry (VBM)13 is a fully automated, unbiased technique that identifies regional differences in brain structure by performing voxel-level comparisons throughout the whole brain. Voxel-based morphometry has been successfully used in the past to document structural brain abnormalities in frontotemporal dementia,14 schizophrenia,15 Kallmann syndrome,16 herpes simplex encephalitis,17 and...
of AD demonstrated significant atrophy of multiple brain regions, including the temporal lobes; however, these studies did not compare the pattern of atrophy seen in AD with that seen in other forms of dementia.

The goal of this study is to identify areas of brain atrophy that may be specific to AD, even when compared with other forms of dementia. As a comparison group we chose patients with semantic dementia (SD), a subtype of frontotemporal lobar degeneration. This is a good comparison group because SD is pathologically distinct from AD but shares several clinical features with AD, including early deficits in language and memory. Semantic dementia is also associated with medial temporal lobe atrophy; however, hippocampal atrophy is more severe in SD than in AD when patient groups are matched for overall level of cognitive impairment.17-21 In contrast to AD, 2 previous VBM studies14,25 of SD showed atrophy that was limited to temporal lobe structures. We hypothesized that regions of cortical atrophy in non–temporal lobe structures would be seen in AD relative to SD, whereas SD would be associated with more severe atrophy of anterior temporal lobe structures in a direct comparison using VBM.

METHODS

PARTICIPANTS

A total of 37 individuals participated in the study: 11 with AD, 11 with SD, and 15 controls. Informed consent was obtained for all components of the study. The diagnosis in the AD and SD groups was made on clinical grounds and not based on MRI findings. Individuals in the SD group met the core criteria for SD described by Neary et al.26 Briefly, these criteria include (1) insidious onset and gradual progression, (2) language disorder (progressive, empty fluent speech and loss of word meaning) or (3) prosopagnosia or associative agnosia, (4) preserved perceptual and drawing reproduction, (5) preserved single-word repetition, and (6) preserved ability to read and write orthographically regular words. Diagnosis of SD does not require formal neuropsychological testing27 and could reliably be made in all patients based on historical information and results of a neurological examination. All of the patients with AD met the probable AD criteria as outlined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.27 In a previous study,21 most of the patients clinically diagnosed as having frontotemporal dementia or AD using these criteria were eventually found to meet pathologic criteria also. The AD group was chosen from a larger cohort of patients with AD to match the SD group in terms of age, sex, education, and Mini-Mental State Examination score.28 Only individuals without significant white matter disease (<2 lacunar infarcts and ≤25% of total white matter volume hyperintensity on T2-weighted MRI) were included in the study. The demographic and neuropsychological profiles of the control and patient groups are given in Table 1.

NEUROPSYCHOLOGICAL TESTS

General intellectual function was assessed using the Mini-Mental Status Examination.28 The California Verbal Learning Test–Mental Status Version29 was used to evaluate verbal episodic memory, and nonverbal episodic memory was measured using a modified version of the Rey-Osterrieth complex figure with a 10-minute free recall delay trial. Language assessment included the abbreviated (15-item) Boston Naming Test,30 comprehension of 7 syntactically complex commands and questions, repetition of 3 phonemically complex phrases, semantic fluency (animals in 1 minute), and phonemic fluency (‘D’ words in 1 minute). Visuospatial assessment included copying the modified Rey-Osterrieth figure and trial 1 of the design fluency subtest of the Delis-Kaplan Executive Functions Scale.31 Tests of executive functioning included a visuomotor set-shifting and sequencing task (a modified version of the Trails B test32), backwards digit span to assess working memory, and the Stroop interference task33 to assess inhibition of an overlearned response. Ability to perform 5 arithmetic calculations was also assessed. Psychological status was measured using a geriatric depression scale.33 Two patients who were diagnosed as having SD by clinical criteria had such significant semantic loss that their comprehension of test instructions was severely compromised, even for nonsemantic tasks. Their testing was considered invalid, and thus none of their neuropsychological data were included in the analyses. A few patients with AD produced invalid data on verbal or executive tests in the battery. For example, because they were unable to produce any words after 4 trials on the California Verbal Learning Test—Mental Status Version, the delayed recall trials could not be administered. Their data on all completed tests were included because they showed evidence of comprehension for test instructions. Ability to complete testing was not related to premorbid English speaking ability.

Group differences in neuropsychological scores were compared using a univariate analysis of variance (ANOVA) statistic, and post hoc comparisons were performed using t tests.34 AND ANOVA statistics revealed that sex and age differences between groups were not significant; thus, no covariates were used in these analyses. Statistical analysis was accomplished using a software package (SPSS version 10.0.5; SPSS Inc, Chicago, Ill).

MRI AND VBM

The MRIs were obtained on a 1.5-T system (Magnetom VISION; Siemens Inc, Iselin, NJ) at the San Francisco Veterans Affairs Hospital Magnetic Resonance Unit, as described in a previous article.21 For this VBM analysis, 3-dimensional T1-weighted (magnetization-prepared rapid acquisition gradient echo) images were preprocessed and statistically analyzed using a statistical parametric mapping software package (SPM99; available at http://www.fil.ion.ucl.ac.uk/spm) and standard procedures.34 The VBM methods used herein are identical to those described in detail in a previous article.34 Briefly, a 12-parameter affine transformation algorithm was used to normalize the images, which were then entered into the VBM analysis. Segmented gray matter images were spatially smoothed with a 12-mm full-width at half-maximum isotropic gaussian kernel. The smoothed gray matter images were normalized to a global mean pixel value of 50 and entered into a design matrix for statistical analysis using the general linear model. Age for each participant was entered into the design matrix as a nuisance variable.

To examine the patterns of atrophy specific to each patient group, the following contrasts were performed:

1. AD vs controls: the areas of gray matter loss in the AD group relative to controls (AD<controls)
2. SD vs controls: the areas of gray matter loss in the SD group relative to controls (SD<controls)
3. SD vs AD: the areas of gray matter loss in the SD group relative to the AD group (SD<AD)
4. AD vs SD: the areas of gray matter loss in the AD group relative to the SD group (AD<SD)

We accepted a statistical threshold of P<.05 at the voxel level, corrected for multiple comparisons, for the main con-
tural imaging data analyzed here.38 tional imaging data of much smaller effect size than the struc-
effects using statistical parametric mapping to analyze func-
to 14 individuals is considered sufficient to demonstrate group
subject to type II error and may not be detected. Analysis of 10
the sample size of 37 individuals, but smaller effects may be
rate to large effect sizes will be detectable by this study given
relations of $r$ = 0.40 if $\alpha$ = .05 is used as the standard. Thus, mod-
are in an enter-method discriminant function analysis to deter-
magnitude and semantic dementia.36

PATIENT CLASSIFICATION

Data reduction was performed by running ANOVA statistics on normalized MRI values from each peak voxel identified in the VBM contrasts (Table 2) to determine which brain areas showed significantly different gray matter concentrations by group. Given that correlations were only expected in one direction for each variable (less tissue content associated with dis-
e, a 1-tailed level of significance ($P < .05$) was accepted. The

RESULTS

One-way ANOVA identified significant group effects for several variables, which were investigated further with post hoc testing (Table 1). Patients with AD and SD performed significantly worse than controls on the Mini-Mental State Examination and on tests of verbal episodic memory (California Verbal Learning Test–Mental Status Version), visuospatial episodic memory (modified Rey-Osterrieth figure recall), executive function (modified Trails, Stroop, and design fluency), phonemic fluency, and semantic fluency. The 2 patient groups showed no significant differences in performance on these tests.

Patients with AD, but not those with SD, scored significantly worse than controls on sentence comprehension ($P = .02$) and phrase repetition ($P = .003$). Patients with AD were more impaired than controls and patients with SD on a test of visuospatial function, the modified Rey-Osterrieth Copy ($P = .02$ vs controls; $P = .04$ vs SD), and calculations ($P < .05$ vs controls; $P = .05$ vs SD). Patients with SD were much more im-


## Table 1. Demographic Characteristics and Neuropsychological Test Results for Patients With AD or SD and Controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>SD Group (n = 11)</th>
<th>AD Group (n = 11)</th>
<th>Controls (n = 15)</th>
<th>Overall ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (n = 37)</td>
<td>66.2 (9.8)</td>
<td>69.6 (8.2)</td>
<td>65.1 (8.3)</td>
<td>$F_{36} = 0.90$</td>
</tr>
<tr>
<td>Education, y (n = 32)</td>
<td>17.4 (3.4)</td>
<td>16.3 (3.8)</td>
<td>16.6 (3.9)</td>
<td>$F_{36} = 0.80$</td>
</tr>
<tr>
<td>Sex, M/F. No. (n = 37)</td>
<td>8/3</td>
<td>8/3</td>
<td>7/8</td>
<td></td>
</tr>
<tr>
<td>MMSE score (max = 30) (n = 36)</td>
<td>21.7 (7.1)†</td>
<td>20.2 (7.3)†</td>
<td>29.5 (0.5)</td>
<td>$F_{36} = 11.11$‡</td>
</tr>
<tr>
<td>CVLT-MS score (max = 9) (n = 28)</td>
<td>4.1 (1.6)†</td>
<td>3.9 (2.1)†</td>
<td>8.4 (0.5)</td>
<td>$F_{36} = 31.81†$</td>
</tr>
<tr>
<td>Trial 4</td>
<td>3.0' Free recall</td>
<td>2.3 (1.4)†</td>
<td>7.7 (1.0)</td>
<td>$F_{36} = 37.73‡$</td>
</tr>
<tr>
<td>10' Free recall</td>
<td>2.6 (2.4)†</td>
<td>1.6 (1.9)†</td>
<td>6.8 (1.2)</td>
<td>$F_{36} = 25.38‡$</td>
</tr>
<tr>
<td>10' Recognition</td>
<td>6.0 (1.9)†</td>
<td>6.9 (1.3)†</td>
<td>8.8 (0.4)</td>
<td>$F_{36} = 13.83‡$</td>
</tr>
<tr>
<td>Modified Rey-Osterrieth delay score (max = 17) (n = 34)</td>
<td>6.4 (5.5)§</td>
<td>3.0 (3.0)†</td>
<td>11.4 (3.3)</td>
<td>$F_{36} = 15.76‡$</td>
</tr>
<tr>
<td>Digit span backwards score (n = 32)</td>
<td>4.4 (1.3)</td>
<td>4.0 (1.0)</td>
<td>5.1 (1.0)</td>
<td>$F_{36} = 3.41‡$</td>
</tr>
<tr>
<td>Modified Trails, No. of lines/min (n = 32)</td>
<td>9.5 (6.3)†</td>
<td>7.0 (6.6)†</td>
<td>33.8 (10.5)</td>
<td>$F_{36} = 35.22‡$</td>
</tr>
<tr>
<td>Stroop, No. correct/min (n = 24)</td>
<td>27.5 (13.7)†</td>
<td>22.5 (8.0)</td>
<td>55.3 (11.7)</td>
<td>$F_{36} = 22.71‡$</td>
</tr>
<tr>
<td>Design fluency score (n = 32)</td>
<td>5.9 (3.0)†</td>
<td>4.3 (3.0)†</td>
<td>11.5 (3.1)</td>
<td>$F_{36} = 18.85‡$</td>
</tr>
<tr>
<td>Phonemic fluency score (n = 32)</td>
<td>7.8 (2.4)†</td>
<td>10.0 (5.7)§</td>
<td>16.0 (5.5)</td>
<td>$F_{36} = 8.41‡$</td>
</tr>
<tr>
<td>Semantic fluency score (n = 33)</td>
<td>5.5 (2.2)†</td>
<td>7.2 (4.9)†</td>
<td>20.1 (3.6)</td>
<td>$F_{36} = 53.27‡$</td>
</tr>
<tr>
<td>Abbreviated BNT score (max = 15) (n = 34)</td>
<td>3.1 (3.0)¶</td>
<td>8.2 (5.2)†</td>
<td>14.5 (0.8)</td>
<td>$F_{36} = 31.87†$</td>
</tr>
<tr>
<td>Sentence comprehension score (max = 7) (n = 32)</td>
<td>6.4 (0.7)</td>
<td>6.0 (1.0)§</td>
<td>6.9 (0.4)</td>
<td>$F_{36} = 4.68‡$</td>
</tr>
<tr>
<td>Phrase repetition score (max = 3) (n = 30)</td>
<td>2.6 (0.5)</td>
<td>2.1 (0.9)†</td>
<td>3.0 (0.0)</td>
<td>$F_{36} = 7.16§$</td>
</tr>
<tr>
<td>Modified Rey-Osterrieth copy score (max = 17) (n = 35)</td>
<td>15.0 (3.8)#</td>
<td>9.7 (6.9)§</td>
<td>14.9 (1.8)</td>
<td>$F_{36} = 5.22‡$</td>
</tr>
<tr>
<td>Calculations score (max = 5) (n = 34)</td>
<td>4.6 (0.7)#</td>
<td>3.6 (1.4)§</td>
<td>4.7 (0.5)</td>
<td>$F_{36} = 5.45‡$</td>
</tr>
<tr>
<td>Geriatric Depression Scale score (max = 30) (n = 29)</td>
<td>10.6 (7.3)</td>
<td>6.6 (8.4)</td>
<td>3.9 (3.2)</td>
<td>$F_{36} = 2.53*$</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ANOVA, analysis of variance; BNT, Boston Naming Test; CVLT-MS, California Verbal Learning Test–Mental Status Version; max, maximum score; MMSE, Mini-Mental State Examination; SD, semantic dementia.

*Data are given as mean (SD) except where indicated otherwise.
†$P < .01$ vs controls.
‡$P < .05$ vs controls.
§$P < .01$ across all groups.
¶$P < .05$ across all groups.
#$P < .01$ vs AD.
$P < .05$ vs AD.

Data are given as mean (SD) except where indicated otherwise.
NEUROIMAGING ANALYSIS

AD vs Controls

This contrast identified regions where atrophy was present in patients with AD relative to controls. The left parietal cortex, the right amygdala/anterior hippocampus, and the left dorsomedial thalamus contained individual voxels that were found to be significantly atrophied (Figure 1 and Table 2). The left parietal cortex showed the most extensive atrophy. Tissue content in this region was more than 2 SDs below the mean of the control group in 9 of 11 patients (Figure 2).

SD vs Controls

Significant atrophy was present in patients with SD relative to controls in the amygdala and anterior hippocampus bilaterally, the left anterior temporal lobe, and the left dorsomedial thalamus (Figure 3 and Table 2). The right amygdala/anterior hippocampus showed the most significant atrophy. Tissue content in this region was more than 2 SDs below the mean in the controls in 10 of 11 patients (Figure 2).

AD vs SD

Significant atrophy was present in the AD group relative to the SD group in the left parietal lobe and the posterior cingulate/precuneus bilaterally (Figure 4 and Table 2). As in the comparison with controls, the left parietal

Table 2. Comparison of Regions of Significant Atrophy in 11 Patients With AD, 11 Patients With SD, and 15 Controls

<table>
<thead>
<tr>
<th>Anatomic Region</th>
<th>Brodmann Area*</th>
<th>X, Y, Z†</th>
<th>Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD vs Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left parietal cortex‡</td>
<td>19/39</td>
<td>−23, 74, 54</td>
<td>5.0</td>
</tr>
<tr>
<td>Right amygdala/anterior hippocampus</td>
<td>NA</td>
<td>26, 5, −24</td>
<td>4.8§</td>
</tr>
<tr>
<td>Left dorsomedial thalamus</td>
<td>NA</td>
<td>−5, −12, 5</td>
<td>4.8§</td>
</tr>
<tr>
<td><strong>SD vs Controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right amygdala/anterior hippocampus‡</td>
<td>NA</td>
<td>24, −2, −21</td>
<td>7.3</td>
</tr>
<tr>
<td>Left amygdala/anterior hippocampus</td>
<td>NA</td>
<td>−26, −3, −26</td>
<td>6.9</td>
</tr>
<tr>
<td>Left anterior temporal lobe</td>
<td>38</td>
<td>−29, 12, −42</td>
<td>6.7</td>
</tr>
<tr>
<td>Left dorsomedial thalamus</td>
<td>NA</td>
<td>−3, −18, 6</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>AD vs SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left parietal cortex</td>
<td>19/39</td>
<td>−21, −72, 54</td>
<td>5.6</td>
</tr>
<tr>
<td>Right posterior cingulate/precuneus‡</td>
<td>23/7</td>
<td>5, −69, 39</td>
<td>5.4</td>
</tr>
<tr>
<td>Left posterior cingulate/precuneus</td>
<td>23/7</td>
<td>−6, −96, 21</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>SD vs AD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right amygdala/anterior hippocampus‡</td>
<td>NA</td>
<td>24, −2, −21</td>
<td>6.7</td>
</tr>
<tr>
<td>Right anterior temporal lobe</td>
<td>38</td>
<td>27, −8, −41</td>
<td>5.3</td>
</tr>
<tr>
<td>Right middle temporal gyrus</td>
<td>21</td>
<td>62, −3, −26</td>
<td>5.3</td>
</tr>
<tr>
<td>Left amygdala/anterior hippocampus</td>
<td>NA</td>
<td>−26, −3, −26</td>
<td>6.2</td>
</tr>
<tr>
<td>Left anterior temporal lobe</td>
<td>38</td>
<td>−29, 12, −42</td>
<td>6.1</td>
</tr>
<tr>
<td>Left temporal pole</td>
<td>38</td>
<td>−50, 12, −23</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; NA, Brodmann designation not available; SD, semantic dementia.
*As indicated by visual comparison with the atlas of Talairach and Tournoux and the atlas of Duvernoy.
†Montreal Neurological Institute coordinates.
‡Used in discriminant function analysis (see the “Results” section).
§P = .08, corrected for multiple comparisons.

Figure 1. Regions of significant tissue loss in the Alzheimer disease (AD) group compared with age-matched controls are superimposed on a normal brain template. Pixels are displayed where atrophy is significant to a level of P < .001. Peaks of significant atrophy after multiple-comparisons correction are listed in Table 2. L indicates left; R, right. Scale bar indicates t test value. A, Left parietal lobe atrophy displayed on a rendered normal brain template from the left lateral and superior views. B, Amygdala/anterior hippocampal atrophy at Montreal Neurological Institute coordinates Y = 5 (coronal) and Z = −24 (transverse). C, Thalamic atrophy at Montreal Neurological Institute coordinates X = −12 (sagittal) and Z = 5 (transverse).

Figure 2. Normalized magnetic resonance imaging values are compared for controls, patients with Alzheimer disease (AD), and patients with semantic dementia (SD) at a right amygdala voxel (Montreal Neurological Institute coordinates X = 24, Y = −2, and Z = −21) found to be more significantly atrophied in SD than in AD (A) and at a left parietal lobe voxel (Montreal Neurological Institute coordinates X = −21, Y = −72, and Z = 54) found to be more atrophied in AD than in SD (B). Horizontal bars indicate the mean ± 2 SD values for the control group.
lobe showed the most significant atrophy when the 2 patient groups were compared. Whereas the tissue gray matter densities in this region were comparable in controls and patients with SD, 10 of 11 patients with AD had less left parietal lobe gray matter than patients with SD (Figure 2).

**SD vs AD**

This contrast identified regions where significant atrophy was present in patients with SD relative to patients with AD. Bilaterally, the amygdalae, hippocampi, and anterior temporal lobes and the right middle temporal gy-
rus and left temporal pole were more atrophied in the SD group than in the AD group (Figure 5 and Table 2). Differences in gray matter concentration between individuals in the 2 patient groups were more pronounced in the left parietal region than in the right amygdala (Figure 2).

**Patient Classification**

An ANOVA identified 4 voxels (right posterior cingulate, left parietal lobe, right amygdala, and right anterior temporal lobe) (Table 2) as showing significantly different gray matter concentrations by group. A discriminant function analysis identified the combination of the gray matter tissue concentrations at these 4 voxels as best able to differentiate the 2 patient groups and controls. Standardized canonical function coefficients for the 4 voxels included in the discriminant function analysis, ordered by decreasing magnitude of contribution, were as follows: right posterior cingulate, 0.668; left parietal lobe, 0.495; right amygdala, 0.317; and right anterior temporal lobe, −0.310. The discriminant function analysis correctly classified 96% of the patients. All 11 patients with SD were correctly classified, whereas 1 patient with AD was misclassified as SD. All of the controls were correctly classified.

**COMMENT**

This study identifies a major difference in the patterns of regional brain atrophy in AD and SD. As such, it further strengthens the potential utility of cinguloparietal measurements in the diagnosis of AD. Compared with controls, both patient groups had evidence of temporal lobe atrophy on T1-weighted MRIs; however, only patients with AD displayed significant parietal lobe atrophy. When cerebral cortical atrophy was directly compared in the 2 patient groups, patients with AD displayed significantly more atrophy in the parietal, precuneus, and posterior cingulate cortices than patients with SD. In contrast, patients with SD displayed significantly more anterior, medial, and lateral temporal lobe atrophy than patients with AD. When gray matter concentrations from 2 right temporal lobe and 2 cinguloparietal voxels were combined in a discriminant function analysis, 96% of the patients were correctly classified as either AD or SD. Of the voxels identified in the discriminant function analysis, the right posterior cingulate and left parietal lobe were most strongly correlated with diagnosis.

Cinguloparietal atrophy is a feature of presymptomatic patients with familial AD, and cinguloparietal hypometabolism found on positron emission tomography with fluorodeoxyglucose may be the earliest metabolic abnormality in AD. Our results complement these studies and suggest that cinguloparietal atrophy may be specific to AD. The demonstration of the left parietal cortex as the most significant area of atrophy in the AD group relative to controls is similar to the results of other volumetric measurements of cortical atrophy in AD that demonstrated similar or greater volume loss in the parietal
cortex and other perisylvian cortical regions than in medial temporal lobe structures.11,12 Posterior cingulate and perisylvian cortical atrophy has also been reported in a “region of interest” volumetric study of AD.13 Finally, a neuropathological study35 of AD showed the greatest decreases in cortical tissue weight relative to controls in the precuneus (53%) and superior parietal lobule (51%).

These results are also consistent with those of 2 other recent VBM studies19,20 of AD-associated brain atrophy. Our study demonstrated areas of atrophy in the left parietal cortex, left dorsomedial thalamus, and medial temporal lobe structures. There are 2 levels of data produced by VBM contrasts. Our analysis used only the least error-prone “voxel-level” inference.13 Had we used “cluster-level” inference, as in the aforementioned studies, our results would have been almost identical to those of one of the previous studies.20 The evidence of medial temporal lobe atrophy seen in the AD group is consistent with a large body of volumetric data showing amygdala and hippocampal atrophy in AD.43,44 Consistent with our results, a recent volumetric study12 of atrophy in AD that focused on limbic structures also demonstrated significant thalamic atrophy.

The comparison of atrophy in AD and SD confirmed the results of recent volumetric studies,23,25 which demonstrated greater volume loss throughout the temporal lobe in SD than in AD. Our data extend these results by demonstrating that the greater degree of brain atrophy in SD relative to AD is limited to the previously identified temporal lobe structures. Similar to other VBM studies23,25 of temporal lobe atrophy in SD, there was significant atrophy of anterior, medial, and lateral temporal lobe structures in our SD patient group.

The patterns of atrophy associated with AD and SD have implications for the neuropsychological abnormalities associated with each disorder. Clinically, AD and SD manifest with memory and language impairment. Consistent with this observation, neuropsychological measurements from the 2 patient groups showed similar degrees of impairment on measures of verbal episodic memory, language, and executive function. There were also significant differences in neuropsychological performance. The greater degree of impairment in the AD group on 2 parietal lobe–dependent tasks, calculations, and copying a complex figure45,46 is reflective of the relative loss of parietal tissue in this group. The overlap in medial temporal lobe atrophy in the 2 patient groups may explain their similar performance on most of the tests of memory in our neuropsychological battery. The more significant atrophy of anterior temporal lobe structures in the SD group relative to the AD group is consistent with the significantly more impaired naming ability in these patients and the critical role of the left anterior temporal lobe in naming tasks.47

This study demonstrates that VBM-based analysis can reveal characteristic patterns of brain atrophy in AD compared with SD and controls. In this sample of clinically defined groups of patients with dementia, regions of VBM-identified atrophy were discriminated between the 2 patient groups with a high degree of accuracy. To better establish the utility of structural neuroimaging methods in the diagnosis of dementia, future studies using VBM and region of interest methods will need to compare patterns of atrophy in AD to those of other forms of neurodegenerative disease such as Lewy body dementia, vascular dementia, and other Pick complex disorders.

Accepted for publication November 19, 2002.

Author contributions: Study concept and design (Drs Boxer, Miller, and Rosen); acquisition of data (Drs Boxer, Rankin, Schuff, Weiner, and Rosen); analysis and interpretation of data (Drs Boxer, Rankin, Miller, Gorno-Tempini, and Rosen); drafting of the manuscript (Drs Boxer, Rankin, and Rosen); critical revision of the manuscript for important intellectual content (Drs Boxer, Miller, Schuff, Weiner, Gorno-Tempini, and Rosen); statistical expertise (Drs Boxer, Rankin, Gorno-Tempini, and Rosen); obtained funding (Drs Miller and Weiner); administrative, technical, and material support (Dr Schuff); study supervision (Drs Miller and Rosen).

This work was supported by the John Douglas French Foundation for Alzheimer’s Research (Los Angeles, Calif), the McBean Foundation, the Sandler Foundation, and the State of California. Dr Boxer is a John Douglas French Foundation Fellow.

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