Measurements of the Amygdala and Hippocampus in Pathologically Confirmed Alzheimer Disease and Frontotemporal Lobar Degeneration

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Background: Differentiating between Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) can be difficult, particularly in the earliest stages of the diseases. Patterns of atrophy on magnetic resonance imaging may help distinguish these diseases and aid diagnosis.

Objective: To assess the diagnostic utility of magnetic resonance imaging–derived amygdala and hippocampal volumes from patients with pathologically proved AD and FTLD.

Design: Cross-sectional volumetric magnetic resonance imaging study of the hippocampus and amygdala.

Setting: Specialist cognitive disorders clinic.

Subjects: Thirty-seven subjects, including 10 patients with pathologically proved AD, 17 patients with pathologically proved FTLD, and 10 age-matched control subjects.

Main Outcome Measures: Hippocampal and amygdala volumes.

Results: Geometric mean amygdala and hippocampal volumes were, respectively, 15.0% (95% confidence interval [CI], 4.2%-24.5%) and 16.4% (95% CI, 5.9%-25.6%) lower in the AD than in the control group. In FTLD, the equivalent differences were 43.1% (95% CI, 31.9%-52.6%) in the amygdala and 36.1% (95% CI, 27.5%-43.7%) in the hippocampus. Volumes were significantly lower in the FTLD than in the AD group (P<.01 in both regions). Within the FTLD clinical subgroups, there was evidence of a difference in pattern of atrophy with greater asymmetry (left smaller than right) in semantic dementia compared with frontal variant FTLD (P<.001). On average, the left hippocampus was 14% smaller in semantic dementia than in frontal variant FTLD, whereas the right hippocampus was 37% larger. On average, the left amygdala was 39% smaller in semantic dementia than in frontal variant FTLD, whereas the right amygdala was only 1% smaller.

Conclusions: Hippocampal atrophy is not specific to AD or FTLD. However, severe or asymmetrical amygdala atrophy should suggest FTLD. Atrophy patterns follow clinical syndromes rather than pathology.

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In the elderly population, Alzheimer disease (AD) is the most common cause of dementia. However, in patients presenting with dementia before age 65 years, the prevalence of frontotemporal lobar degeneration (FTLD) approximates that of AD. Differentiating AD from FTLD is important because the prognoses and management of these diseases are different. A diagnosis of AD is suggested if memory decline is an early clinical feature, whereas prominent behavioral and language dysfunction suggests a diagnosis of FTLD. However, recent clinicopathological studies have identified cases of FTLD with prominent episodic memory loss, and a frontal presentation of AD has been described. The overlap in clinical features and diagnostic uncertainty, especially in the early stages, has led to interest in imaging studies to help differentiate FTLD from AD. Prominent hippocampal atrophy has been demonstrated to be the signature pattern of atrophy on magnetic resonance imaging (MRI) studies in AD, whereas more anterior temporal losses, including severe amygdala atrophy, have been suggestive of FTLD. These findings support the clinical presentations because hippocampal damage is linked to loss of episodic memory, and amygdala damage has been associated with emotional and behavioral dyscontrol. Pathology remains the gold standard in the diagnosis of AD and FTLD. Although several MRI studies have examined the ability of volumetric measures to differentiate clinically diagnosed FTLD.
from AD, clinical diagnostic accuracy is uncertain in the absence of histopathological confirmation, and potential exists for circularity in study design. Therefore, this study assessed the value of hippocampal and amygdala measurements in separating patients with AD and FTLD from control subjects and from one another in a pathologically defined cohort of AD and FTLD cases.

METHODS

SUBJECTS

Patients were recruited from the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery. Ten patients with pathologically confirmed AD and 17 patients with pathologically confirmed FTLD (3 with Pick disease, 8 with ubiquitin-only immunoreactive neuronal inclusions [FTLD-U], 3 tau positive with tau exon 10 + 16 mutations [tau exon 10 + 16], and 1 with dementia lacking distinctive histology [DLDH]) were included in this study. Pathological diagnosis was based on the most recent consensus criteria.25 Pathological confirmation by biopsy rather than postmortem findings was available in 4 of the patients with AD and 2 of the patients with FTLD.

We reviewed medical records and recorded the clinical presentation, disease duration, and Mini-Mental State Examination score at the time of the MRI study. A family history of dementia was present in all cases of tau exon 10 + 16, 2 cases of FTLD-U, and 1 case of AD. We used established clinical criteria to classify the patients with FTLD into frontotemporal variant FTLD (fvFTLD) (n=12), semantic dementia (SD) (n=4), and progressive nonfluent aphasia (n=1).22 None of the patients with FTLD had any clinical evidence of motor neuron disease. Ten healthy age-matched controls without evidence or symptoms of cognitive decline were also included in the study. The demographic characteristics of all subjects are reported in Table 1.

IMAGE ANALYSIS

Image Acquisition

The MRI studies were performed on a 1.5-T imaging system (GE Signa Unit; General Electric Medical Systems, Milwaukee, Wis) using a spoiled gradient-echo technique (256 × 128 matrix; field of view, 24 × 19.2 cm; repetition time, 35 milliseconds; echo time, 5 milliseconds; number of excitations, 1; and flip angle, 35°; yielding 124 contiguous 1.5-mm-thick sections). If an individual had more than 1 diagnostic imaging study, the earliest one was chosen for inclusion in the study.

Manual Segmentation

The MIDAS software package was used for all imaging analysis and allows tracing of regions of interest in 2 orthogonal views.26 Before tracing, all images were registered to a standard template.27 In addition, each image was reflected across the midsagittal plane, and traces were performed on the right side of the presented image. The operators (J.B. and J.L.W.) were blinded to the subject’s identity and diagnosis and to the left-right orientation of the image.

Amygdala28 and hippocampal29 measurements were performed as previously described. Intrarater variability (expressed as an intraclass correlation coefficient) was 0.98 in the hippocampus and 0.98 in the amygdala. This measure of variability was based on 20 hippocampi and 12 amygdala having been segmented twice by the same rater (J.B. and J.L.W., respectively).

STATISTICAL ANALYSIS

We analyzed the data using STATA version 8 (StataCorp, College Station, Tex) and SAS (SAS Institute Inc, Cary, NC) statistical software. Volumes were adjusted for head size differences using the total intracranial volume, derived according to a previously described protocol.30 Standardization was carried out separately for the amygdala and hippocampus. For both structures, this assumed a linear relationship between log-transformed values and log-total intracranial volume, with the slopes of the associations estimated from left and right measurements in an expanded control group to improve precision.31

To minimize the number of hypothesis tests performed, we carried out a structured analysis using linear mixed models with interaction terms and disease group–specific unstructured covariance matrices. Such an approach extends analysis of variance by removing the requirement for homogeneity of variances. Such models were used to make comparisons between geometric mean volumes by (1) disease group (FTLD vs AD vs control group in the primary analysis), (2) amygdala vs hippocampus, and (3) structural laterality. We used contrasts of mean levels to estimate effect sizes and Wald tests to examine the statistical significance of interaction terms and main effects. We also used models of this type to compare geometric mean volumes by FTLD subtype. Because unstructured covariance models do not facilitate comparison of variances between disease groups and regions, direct-product covariance matrices (amygdala/hippocampus × left/right side) were used to compare variances between (1) disease groups, (2) structures (amygdala and hippocampus), and (3) left and right sides. A likelihood ratio test was used to compare the fit of a model where the disease group–specific amygdala and hippocampal variances were assumed constant with those of one where they were allowed to be different. A similar approach was used to compare left- and right-sided variances. In a similar comparison of variances by disease groups, we assumed left- and right-side variances to be the same. In addition, we calculated sensitivities for certain specificity cutoffs to test the relative utility of both structures in discriminating subject groups.

RESULTS

There was no significant difference in age or sex distributions between the FTLD, AD, and control groups (Table 1). Mini-Mental State Examination scores were
significantly higher in the control group than in the AD and FTLD groups (\(P < .003\)) and significantly higher in the FTLD group than in the AD group (\(P = .03\)). There was no significant difference in disease duration and time to death between the FTLD and AD groups.

Hippocampal and amygdala volumes from the 3 subject groups are shown in Table 2 and displayed as scatterplots in Figure 1. Analysis using linear mixed models on log-transformed values showed no evidence (\(P > .2\) for all comparisons) that proportionate differences in volumes between the disease groups differed between the amygdala and hippocampus and/or between the hemispheres, or that proportionate differences in the volumes between the hemispheres differed between the amygdala and hippocampus. When left and right regions were averaged, the geometric mean amygdala and hippocampal volumes were, respectively, 15.0% (95% confidence interval [CI], 4.2%-24.5%) and 16.4% (95% CI, 5.9%-25.6%) lower in the AD than the control group. In the FTLD group, the equivalent differences were 43.1% (95% CI, 31.9%-52.6%) in the amygdala and 36.1% (95% CI, 27.5%-43.7%) in the hippocampus. The difference in volumes between the FTLD and AD groups was statistically significant (\(P < .01\) in both regions).

There was no evidence (\(P > .2\)) that the direct-product unstructured covariance matrices did not provide a good fit to the data. Such models demonstrated that variability in the amygdala and hippocampal volumes relative to the mean levels was greater in the FTLD group than in the AD group and greater in the disease groups than the control group (\(P < .001\) for all cases vs controls; \(P = .02\) for AD vs FTLD group, jointly modeling both structures), as suggested by the coefficients of variation reported in Table 2. There was no evidence of differences in variability between the amygdala and hippocampal volumes (jointly modeling left and right sides and the disease groups) or between structures on the left and right sides (jointly modeling disease groups and structures).

As anticipated from the comparison of the means, all 4 volumes (the left and right hippocampus and left and right amygdala) could significantly discriminate the patients with AD (vs controls) and patients with FTLD (vs controls and patients with AD) by using regression models (\(P < .05\)). When the specificity was set at 80%, the sensitivity for detection of the patients with AD from the controls ranged from 65% in the right amygdala to 80% in the left amygdala, with both hippocampal measures falling within this range. In comparison, the sensitivity for detection of patients with FTLD from controls was more than 90% in all structures and reached 100% in the right hippocampus. In addition, for a specificity of 80%, the right amygdala could discriminate patients with FTLD and pa-

### Table 2. Volumes of TIV-Adjusted Hippocampus and Amygdala

<table>
<thead>
<tr>
<th>Subject Groups</th>
<th>Control</th>
<th>AD</th>
<th>FTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left Side</td>
<td>Right Side</td>
<td>Left Side</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Mean (95% CI)</td>
<td>1555 (1491-1619)</td>
<td>1618 (1514-1721)</td>
</tr>
<tr>
<td>SD</td>
<td>89</td>
<td>144</td>
<td>260</td>
</tr>
<tr>
<td>CV*</td>
<td>5.7</td>
<td>8.9</td>
<td>19.6</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Mean (95% CI)</td>
<td>2898 (2723-3073)</td>
<td>2967 (2727-3207)</td>
</tr>
<tr>
<td>SD</td>
<td>245</td>
<td>336</td>
<td>449</td>
</tr>
<tr>
<td>CV*</td>
<td>8.5</td>
<td>11.3</td>
<td>18.6</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CI, confidence interval; CV, coefficient of variation; FTLD, frontotemporal lobar dysfunction; TIV, total intracranial volume.

*Calculated as 100 \(\times\) (SD/mean).
tients with AD with a sensitivity of 88%, whereas the sen-
sitivity for the other 3 structures ranged from 50% to 71%.

SUBGROUPS OF FTLD

The FTLD group was subdivided pathologically into those
with FTLD-U, tau exon 10 +16, Pick disease, and DLDH.
Owing to the presence of only 1 subject in the DLDH
group, this group was removed from the pathological sub-
group analysis. There was no evidence of differences in
the mean hippocampal or amygdala volumes among the
3 remaining groups (P>.5).

The FTLD group was also subdivided clinically into
to those with fvFTD, SD, and progressive non fluent apha-
sia. The amygdala and hippocampal volumes in these
subgroups are shown in Figure 2. Because only 1 indi-
vidual was in the progressive non fluent asha group,
this group was removed from further analysis. There
was evidence that the ratio of the geometric mean vol-
umes in the 2 subtypes differed between the amygdala
and hippocampus (P=.02) and by hemisphere
(P<.001). On average, the left hippocampus was 14% smaller in the SD subgroup than in the fvFTD sub-
group, whereas the right hippocampus was 37% larger.
On average, the left amygdala was 39% smaller in the
SD subgroup than in the fvFTD subgroup, whereas the
right amygdala was only 1% smaller. These differences
can be seen graphically in Figure 3, which represents
the area per section along the length of the union of the
hippocampal and amygdala regions. These profiles also
show the relatively greater involvement of the anterior
regions compared with the posterior regions in the
fvFTD and SD subgroups, compared with the patients
with AD and the controls.

This study examined the patterns of amygdala and hip-
pocampal atrophy in pathologically confirmed cases of
FTLD and AD. Volumes of these structures were re-
duced in both the FTLD and AD groups compared with
the controls, consistent with previous studies. In addi-
tion, the volumes of both structures were smaller in the
FTLD than in the AD group; the amygdala was re-
duced by 43% and the hippocampus by 36% in the FTLD
compared with the control group, compared with only
15% and 16%, respectively, in the AD group. Atrophy of
the hippocampus is clearly not specific to AD. Indeed,
severe patterns of hippocampal atrophy, especially if as-
associated with severe amygdala atrophy or asymmetry, are
suggestive of FTLD.
Previous MRI studies have found greater or similar degrees of hippocampal atrophy in AD compared with FTLD, although atrophy was predominantly located in the more anterior portions of the hippocampus in FTLD. However, severe patterns of focal lobar atrophy are observed in FTLD post mortem; gyri are often so thin that they have a knife-blade appearance. Therefore, it is perhaps unsurprising that medial temporal lobe structures such as the amygdala and hippocampus may be severely affected. Furthermore, hippocampal sclerosis is common in FTLD. The finding of smaller amygdala volumes in FTLD than in AD is consistent with data from clinically defined groups. Another study reported the amygdala to be larger in FTLD than in AD, although the AD group in that study was nearly a decade older than the FTLD group.

Measurements of the hippocampus and amygdala provided good discrimination of patients with FTLD and those with AD from the controls. The specificity of 80% and sensitivity of 75% for discrimination of patients with AD from the controls using the (left) hippocampal volume is similar to those of previous hippocampal studies. The discrimination of patients with FTLD from the controls was achieved with a specificity of 80% and sensitivities of greater than 90% for all structures, reaching 100% for the right hippocampus, which is superior to that found in some studies. (Comparisons between studies are difficult, however, because of differences between subject groups (especially because pathological evidence of disease is often lacking) and differences in severity of disease at the time of the scan. Previous studies have found poor discrimination between AD and FTLD using single volumetric measures. This study, however, suggested that for a specificity of 80%, the right hippocampus and amygdala could differentiate FTLD from AD with sensitivities of greater than 70%. This improved discrimination is likely to be a result of this study using a pathologically confirmed cohort because recent studies suggest that only 63% to 79% of pathologically confirmed FTLD cases are correctly classified clinically on their first assessment.

In our FTLD subgroup analysis, we did not find a clear differential pattern of amygdala and hippocampal atrophy by pathological subtype. This finding is consistent with that of a previous study, which showed medial temporal lobe atrophy in all 3 pathological subtypes. However, when dividing our FTLD group by clinical subtype, we found marked differences in the patterns of atrophy. First, the SD subgroup showed a more asymmetrical pattern of atrophy than did the fvFTD subgroup with much greater atrophy on the left side; second, the SD subgroup had disproportionately smaller amygdala volumes compared with the hippocampus than did the fvFTD subgroup. These findings are consistent with those of previous volumetric studies in patients clinically diagnosed as having SD or fvFTD that have shown asymmetrical temporal lobe atrophy with particularly severe amygdala atrophy in SD and relatively symmetrical atrophy in fvFTD. These findings support the idea that the clinical phenotype in FTLD more closely reflects the pattern of tissue loss than does the molecular pathology of the diseases. Semantic dementia and fvFTD also showed relatively greater involvement of the anterior than the posterior regions of the amygdalohippocampal structure. This posterior-anterior gradient has been previously reported in patients with SD.

The main strength of this study is the pathological confirmation of disease in all cases. However, a limitation of using a pathologically defined patient group is that the study may be biased toward the cases that were difficult to diagnose during life. Another limitation with all studies of this type is that of accurately matching the patients in the AD and FTLD groups for disease severity. Although the Mini-Mental State Examination has been useful as a measure of disease severity in AD, it is a less comparable measure in FTLD. Owing to this potential problem, we also assessed the disease duration of all patients. The AD and FTLD groups had a similar mean disease duration of approximately 3 years. Finally, the patient groups were also relatively small in this study. Therefore, more subtle differences that may exist in hippocampal and amygdala atrophy between AD and FTLD, and between the pathological and clinical subgroups of FTLD, may not have been detected.

In conclusion, we have shown that both the hippocampus and amygdala are reduced in volume in pathologically confirmed cases of AD and FTLD compared with controls, with the greatest loss shown in patients with FTLD. This finding demonstrates that (1) hippocampal atrophy is not specific to AD and (2) severe or asymmetrical patterns of amygdala and hippocampal atrophy suggest pathological FTLD. The hippocampus and amygdala provide good discrimination of disease groups from controls and between disease groups.

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REFERENCES


