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Amygdalohippocampal MR Volume Measurements in the Early Stages of Alzheimer Disease

Stéphane Lehericy, Michel Baulac, Jacques Chiras, Laurent Piérot, Nadine Martin, Bernard Pillon, Bernard Deweer, Bruno Dubois, and Claude Marsault

PURPOSE: To evaluate the accuracy of hippocampal and amygdala volume measurements in diagnosing patients in the early stages of Alzheimer disease. **METHODS:** Measurements of the hippocampal formation, amygdala, amygdalohippocampal complex (the two measurements summed), caudate nucleus, and ventricles, normalized for total intracranial volume, were obtained on coronal sections (1.5 T, 400/13 [repetition time/echo time], 5 mm) of 13 patients in the mild (minimetal status ≥ 21) and five patients in the moderate stages of Alzheimer disease ($10 < \text{minimetal status} < 21$), and eight age-matched control subjects. **RESULTS:** For patients with a minimetal status score of 21 or greater, atrophy was significant for the amygdala and hippocampal formation (-36% and -25% for amygdala/total intracranial volume and hippocampal formation/total intracranial volume, respectively), but not for the caudate nucleus. No significant ventricular enlargement was found. For patients with a minimetal status score less than 21, atrophy was more severe in all structures studied (amygdala/total intracranial volume, -40% ; hippocampal formation/total intracranial volume, -45% ; caudate nucleus/total intracranial volume, -21%), and ventricles were enlarged (63%). No overlap was found between Alzheimer disease and control values for the amygdalohippocampal volume, even in the mild stages of the disease. In Alzheimer disease patients, hippocampal formation volumes correlated with the minimetal status. **CONCLUSION:** Hippocampal and amygdala atrophy is marked and significant in the mild stages of Alzheimer disease. Volumetric measurements of the amygdala and the amygdalohippocampal complex appear more accurate than those of the hippocampal formation alone in distinguishing patients with Alzheimer disease.

Index terms: Dementia; Hippocampus; Brain, magnetic resonance; Brain, measurements; Brain, volume

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A definite diagnosis of Alzheimer disease depends on the neuropathologic evidence of senile plaques, neurofibrillary tangles, and cell loss (1-3) that predominate in the hippocampus, entorhinal cortex, and amygdala (3-6). Neuropathologic

studies have shown the overall accuracy of the clinical criteria currently used for the diagnosis of Alzheimer disease (7, 8) to be 81% to 88%, depending on the neuropathologic criteria used (9). However, the diagnosis is not as accurate for the early and/or mild stages of Alzheimer disease, in which cognitive and memory deficits may be difficult to distinguish from age-related cognitive dysfunction (10). This may have some important implications for prognosis, therapy, or research.

Imaging techniques may be useful in the diagnosis of Alzheimer disease. Cell loss results in atrophy (11, 12), so computed tomographic (CT) studies have evaluated cerebral atrophy in patients with Alzheimer disease (estimated by ventricular size, cerebrospinal fluid spaces, sulcal width, and/or ventricle/brain ratio); but they have

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failed to differentiate these patients from elderly control subjects given the great overlap between ratings (13). Moreover, these parameters evaluate only global cerebral atrophy (13), whereas the most severely involved areas are in the medial temporal lobe. Magnetic resonance (MR) has been shown to be accurate in measuring hippocampal volume (14). Indeed, MR-based volume measurements of the hippocampal formation have shown a marked and significant atrophy in patients with Alzheimer disease compared with control subjects (15, 16), indicating that MR might give useful diagnostic information (15–17). However, these studies focused on the hippocampal formation and may have therefore overshadowed the possible implication of other limbic structures such as the amygdala. Moreover, no distinction was made between patients with mild dementia and those in the moderate stages of the disease, even though diagnostic uncertainties are most prominent in the mild stages of the disease.

The aim of the present study was: 1) to compare the extent of the atrophy of the hippocampal formation and the amygdala in the mild and the moderate stages of Alzheimer disease; 2) to evaluate the accuracy of hippocampal-formation and amygdala volume measurements in differentiating patients with Alzheimer disease from age-matched control subjects; and 3) to assess the specificity of the involvement of the hippocampal formation and amygdala, by comparison with caudate nucleus and ventricular enlargement.

Patients and Methods

Populations

We studied 18 patients with probable Alzheimer disease (mean age, 72.4 ± 1.5 years) and 8 age-matched control subjects (mean age, 69.2 ± 2.7 years, $P = 0.28$). Patients with Alzheimer disease and control subjects were recruited by means of the Memory Clinic of the Hôpital de la Salpêtrière. Patients with Alzheimer disease were submitted to neurologic, neuropsychologic, and psychiatric examination and fulfilled all the National Institute of Neurological and Communicative Disorders and Stroke-ADRDA work group criteria (8). All patients had normal results of neurologic examination and serum analysis, including thyroidian hormones, vitamin B12, folates, and syphilis serology, and CT scans showed no significant abnormalities. In order to exclude vascular and/or mixed dementia, we made sure that ischemic scores were not greater than four in any patient or control subject (18). This score included features such as acute onset and focal neurologic signs shown to correlate with ischemic changes in the brain (scale range, 0 to 18; the higher the score the greater the probability of ischemic dementia).

From the score of the minimal status examination (MMSE) (19), patients with Alzheimer disease were divided into two groups according to the severity of cognitive dysfunction: 1) those with mild dementia, defined by an MMSE score of 21 or greater (mean MMSE score = 24.1 ± 0.6 , $n = 13$); and 2) those with moderate dementia, defined by an MMSE score between 10 and 20 (inclusive) (mean MMSE score = 16.6 ± 0.9 , $n = 5$, lowest MMSE score = 13). Mean duration of the disease was 2.4 ± 0.3 years. Control subjects had no history of neurologic or psychological illness. Their mean MMSE score was 28.7 ± 0.4 . All the control subjects had a Global Deterioration Scale rating of 1 (20). This scale delineates the stages of primary degenerative dementia. Stage 1 indicates no cognitive decline, thereby excluding cognitive dysfunction in the control subjects. All control subjects gave informed consent. None of the patients with Alzheimer disease or the control subjects had clinical evidence of stroke or of cortical infarction on the T2-weighted MR images (this was an exclusion criterion). MR studies were done within one week of the neuropsychologic evaluation.

MR Examination

All studies were performed on a 1.5-T MR unit. After a scout sequence to ensure symmetric positioning of the subject's head, three series of scans were taken at each examination: 1) sagittal, T1-weighted (6-mm section thickness, 2.5-mm gap); 2) oblique coronal, T1-weighted (spin-echo, 400/13/2 [repetition time/echo time/excitations], field of view 24 cm, 256×192 matrix, 5-mm section thickness, no gap); and 3) coronal, T2-weighted (spin-echo, 2500/30–90, 6-mm section thickness). The oblique coronal plane imaging sequence was acquired perpendicular to the long axis of the hippocampus (maximum anatomic delineation of the hippocampal formation), which was defined on the sagittal images (Fig 1). One section was chosen to include the anterior commissure. Therefore, this coronal section was matched to a corresponding section in the

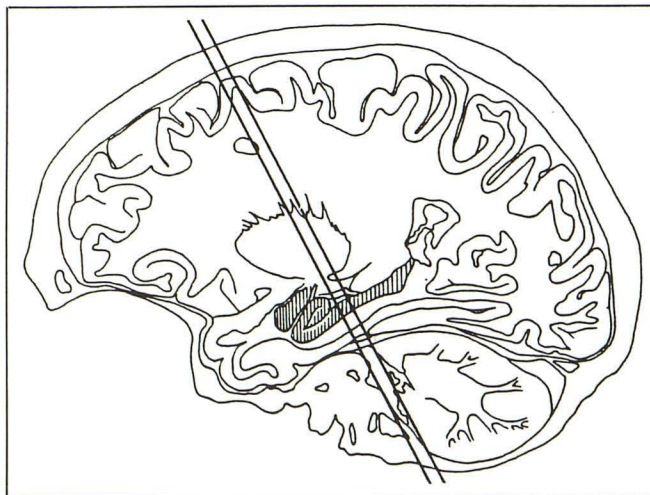


Fig. 1. Definition of the oblique coronal plane perpendicular to the long axis of the hippocampal formation.

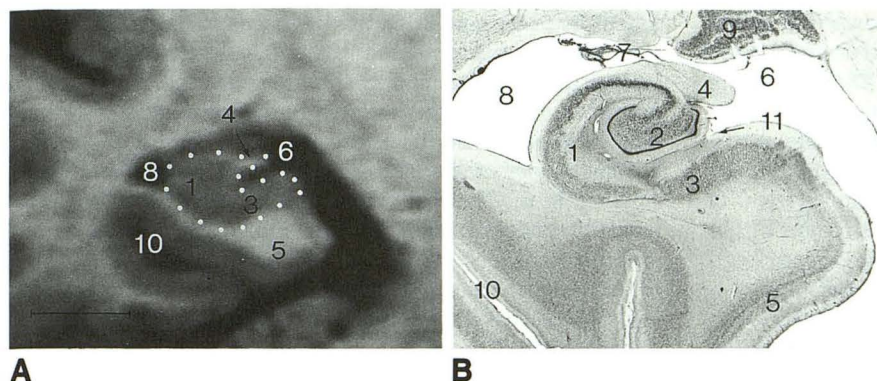


Fig. 2. Comparison of coronal oblique MR scan in one control brain (A) and histologic section (B) at the level of the body of the hippocampal formation. The hippocampal formation is outlined on the MR scan. 1 indicates Ammon's horn; 2, dentate gyrus; 3, subiculum; 4, fimbria; 5, parahippocampal gyrus; 6, transverse (choroid) fissure; 7, choroid plexuses; 8, temporal horn; 9, lateral geniculate body; 10, collateral sulcus; and 11, hippocampal sulcus (scale bar, 1 cm).

other brains, to minimize partial volume averaging at the level of the uncus, in line with already described methods (15, 16). Scans were first evaluated by a neuroradiologist to determine whether any abnormalities would exclude the subject from the study.

Volumetric Measurements

MR images were analysed using an image-analysis system (HISTO-RAG, BIOCOM, France). The software uses a semiautomated technique combining tracing and thresholding. Quantitative volume estimates of the hippocampal formation (HF), the amygdala (A), the caudate nucleus (CN), and the ventricles (V) (consisting of the lateral plus the third ventricles) were obtained on the T1-weighted coronal oblique images providing high gray matter and white matter and brain/CSF contrast. Images were contiguous. Values were also calculated for the amygdalo-hippocampal complex (AHC), which included the hippocampal formation and the amygdala taken together, in order to avoid eventual imprecisions in the delineation of the hippocampal formation from the amygdala. Regions of interest that presented high gray scale contrast (brain-CSF interface) were defined by a gray scale threshold (ventricular volume). Regions of interest that did not present a gray scale contrast high enough to allow thresholding were manually traced with a mouse-driven cursor (hippocampal formation, amygdala, and caudate nucleus). The surface areas of all regions of interest were automatically calculated and the volume of each structure derived by multiplying that value by the intersection distance. Region of interest delineation and volume measurements were performed by an operator (S.L.) with extensive experience with the BIOCOM HISTO-RAG software (21, 22). The operator was unaware of the clinical diagnosis.

Volumes were adjusted for total intracranial volume (TIV). TIV was evaluated by tracing the outline of the inner table on every sagittal image from side to side of the head, multiplying each surface obtained by intersection distance (6 mm) and adding all the sections. Values of each structure were normalized for intersubject variation in head size by dividing each value obtained by the subject TIV. This method has already been used in CT (23) and MR studies (16). Thus, HF/TIV, A/TIV, AHC/TIV, and CN/TIV are

ratios expressing the mean of the left and right sides of HF, A, AHC, and CN, divided by the TIV for each patient. V/TIV is a ratio expressing the volume of the lateral ventricles plus the third ventricle as a percentage of TIV for each patient. Values are expressed as mean $\pm$ SEM. Statistical analyses were done with Student's *t* test.

Histology

To determine accurate and reproducible boundaries, oblique coronal MR images of the hippocampal formations and the amygdala were compared with histologic sections obtained from the brain of one control subject, who died without known neurologic or psychologic illness. The brain was fixed in paraformaldehyde for 3 months, hemisected, and cut into 1-cm slabs. Blocks of tissue containing the hippocampal formation and the amygdala were frozen and cut into serial coronal sections (100 μ m) on a freezing microtome. The plane of section was perpendicular to the long axis of the hippocampal formation. Glass-mounted sections were stained with the cresyl-violet technique and coverslipped.

Hippocampal Formation, Amygdala, and Caudate Nucleus Boundaries

Boundaries of the hippocampal formations and the amygdala were drawn on coronal MR images by comparison with histologic sections obtained in the same plane perpendicular to the long axis of the hippocampus (Figs 2–6), according to the criteria of Duvernoy (24) and other neuroanatomy atlases (25–28). Boundaries were defined as follows.

Measurements of the hippocampal formations at the level of the body of the structure (approximately four to five sections, spanning a rostrocaudal extent of about 3 cm) were generally easy. These measurements included Ammon's horn, the subiculum, the dentate gyrus, and the white-matter tracts of the alveus and the fimbria (Figs 2 and 3). The limit between the subiculum and the parahippocampal gyrus was arbitrarily defined by a line in continuation with the inferior border of the subiculum. Measurements at the level of the tail and the head of the hippocampal formations were more difficult. Caudally, the posterior

boundary of the hippocampal formation was chosen as the last section containing Ammon's horn, which corresponded to the section where the crus of the fornix was visible (Fig 4). Measurements at this level (one section) included the subiculum, the hippocampal formation, the dentate gyrus, the alveus, and the fimbria, and excluded the parahippocampal gyrus and the isthmus of the cingulate gyrus (Fig 4). Rostrally, the head of the hippocampal formation within the posterior part of the uncus was delineated from both the amygdala and the parahippocampal gyrus (approximately two sections, Figs 5 and 6). This delineation was guided by visualizing either the characteristic shape of the hippocampal digitations and the uncus recess of inferior horn of the lateral ventricle (Fig 5), or the band of high

signal intensity generated by the alveus, which demarcated the hippocampal head from the overlying amygdala. When neither the digitations and the uncus recess of the lateral ventricle nor the alveus were visible, the limit was arbitrarily drawn as an horizontal line connecting the middle of the medial border of the lateral ventricle to the surface of the uncus (Fig 6). This limit was chosen after careful comparison with histologic sections. The subiculum of the uncinate gyrus was part of the measurements (Fig 5).

Amygdala measurements (three to four sections, Figs 5 and 6) included the corticomедial, central, and basolateral subgroups and the gyrus semilunaris that covers the cortical nucleus (25). The medial border of the amygdala is partly covered by the entorhinal cortex, which forms the

Fig. 3. Comparison of coronal oblique MR scan in one control brain (A) and histologic section (B) at the level of the body of the hippocampal formation, caudal to Figure 2. The hippocampal formation is outlined on the MR scan. 1 indicates Ammon's horn; 2, dentate gyrus; 3, subiculum; 4, fimbria; 5, parahippocampal gyrus; 6, transverse (choroid) fissure; 7, choroid plexuses; 8, temporal horn; and 9, collateral sulcus (scale bar, 1 cm).

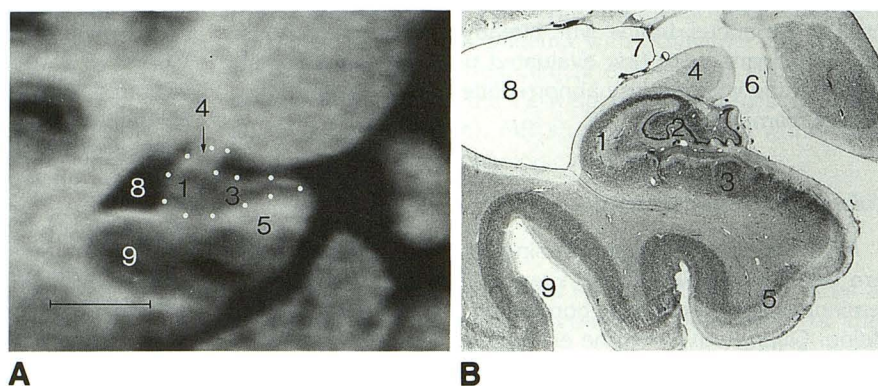


Fig. 4. Comparison of coronal oblique MR scan in one control brain (A) and histologic section (B) at the level of the tail of the hippocampal formation. The hippocampal formation is outlined on the MR scan. 1 indicates Ammon's horn; 2, dentate gyrus; 3, gyrus fasciolaris; 4, fimbria; 5, parahippocampal gyrus; 6, gyrus of Andreas Retzius; 7, calcarine sulcus; 8, lateral ventricle; 9, isthmus; and 10, collateral sulcus (scale bar, 1 cm).

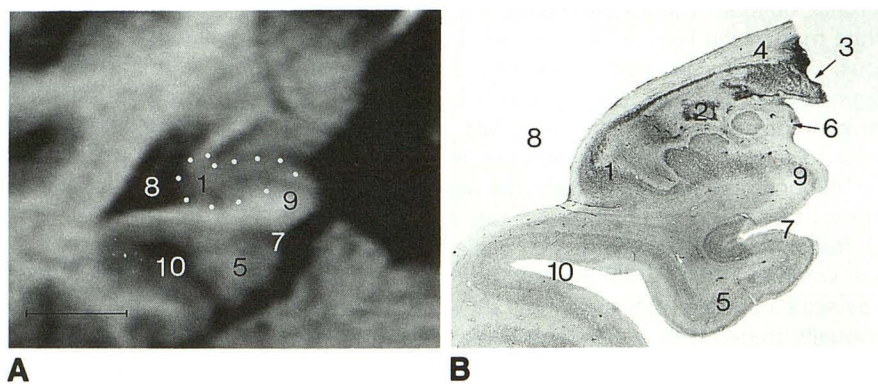
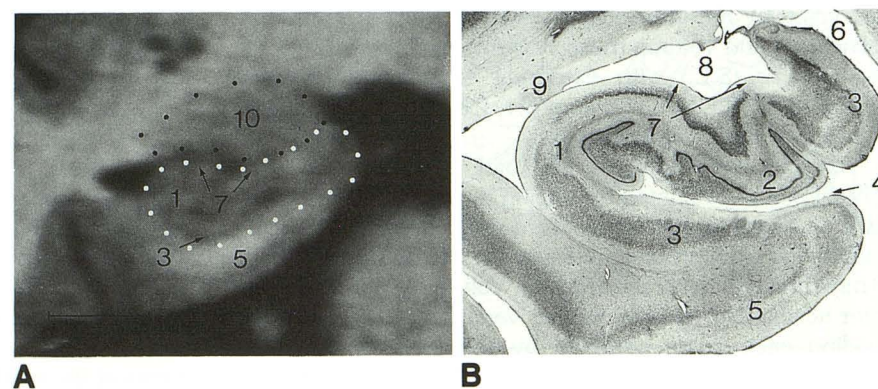


Fig. 5. Comparison of coronal oblique MR scan in one control brain (A) and histologic section (B) at the level of the head of the hippocampal formation. The hippocampal formation (white dots) and the amygdala (black dots) are outlined on the MR scan. 1 indicates Ammon's horn; 2, dentate gyrus; 3, subiculum; 4, hippocampal sulcus; 5, parahippocampal gyrus; 6, transverse (choroid) fissure; 7, hippocampal digitations; 8, temporal horn; 9, tail of the caudate nucleus, and 10, amygdala (scale bar, 1 cm).



surface of the gyrus ambiens (Fig 6). The entorhinal cortex corresponds to area 28 of Brodmann and constitutes a major part of the anterior parahippocampal gyrus (24). The gyrus ambiens was separated from the parahippocampal gyrus by the uncus notch (produced by the free edge of the tentorium cerebelli) (Fig 6). Measurements included the cortex of the gyrus ambiens, which could not be accurately separated from the amygdala, and excluded the entorhinal cortex inferior to the uncus notch. When the uncus notch was poorly or not at all visible in the anterior amygdaloid area, the demarcation between the amygdala and the entorhinal cortex was defined by a line in continuation with the inferior border of the amygdala, thus probably including a small part of the entorhinal cortex. The inferior and lateral borders of the amygdala were formed by the lateral ventricle or the white matter of the temporal lobe and were easily demarcated (Figs 5 and 6). The superior border of the amygdala was not clear-cut. Therefore, the amygdala was demarcated from the above substantia innominata by a horizontal line, arbitrarily passing at the bottom of the entorhinal sulcus (Figs 5 and 6). At its posterior end, the optic tract delimited the medial and superior borders of the amygdala. At this level, the superior border was defined by a horizontal line passing at the superolateral aspect of the optic tract.

This method probably excluded small amounts of the medial and central nuclei, but it is reproducible and easy to determine. The amygdala was also usually well demarcated from the tail of the caudate nucleus and the putamen. The anterior pole of the amygdala was the most difficult to delineate in part because of partial voluming. Thus, the most anterior section measured was arbitrarily defined as the section at the level of the closure of the lateral sulcus to form the entorhinal sulcus, as previously described (28). Rostrally, it was not possible to delineate accurately the amygdala from the surrounding areas such as the prepyriform cortex and the entorhinal cortex. The section including the anterior commissure contained part of the hippocampal head and the posterior part of the amygdala (Fig 5). The two or three sections forward were analyzed mainly for the amygdala, whereas the seven or eight sections backward were analyzed for the hippocampal formation. The volume of the caudate nucleus was estimated on the first nine sections in which it was contained, from the

TABLE 1: Volume measurements in patients with Alzheimer disease and in control subjects (in cm^3)

	Control (n = 8)	Alzheimer (n = 18)
TIV	1245 $\pm$ 75	1309 $\pm$ 11
V	26.9 $\pm$ 4.6	35.6 $\pm$ 3.4
HF (r)	3.01 $\pm$ 0.08	2.19 $\pm$ 0.10
(l)	2.88 $\pm$ 0.09	2.11 $\pm$ 0.10
A (r)	2.24 $\pm$ 0.15	1.47 $\pm$ 0.06
(l)	2.16 $\pm$ 0.11	1.38 $\pm$ 0.05
CN (r)	3.38 $\pm$ 0.12	3.10 $\pm$ 0.12
(l)	3.35 $\pm$ 0.13	3.05 $\pm$ 0.10

Note.—TIV indicates total intracranial volume; V, ventricles; HF, hippocampal formation; A, amygdala; and CN, caudate nucleus.

anterior pole of the head to the posterior part of the body of the nucleus. Boundaries of the caudate nucleus were easily demarcated from the surrounding structures.

Results

Volume measurements of the ventricles, hippocampal formation, amygdala, caudate nucleus and the total intracranial volume are presented in Table 1, for both control subjects and patients with Alzheimer disease. In the control subjects, mean volume of the right hippocampal formation was larger than mean volume of the left side (mean right-left difference = 0.15 cm^3), but the difference was not significant ($P = .26$). No significant volume difference between right and left amygdala was observed. Repeated measures obtained on the same subjects were close, with less than 10% intraobserver variation.

Normalized volumes and percentage decrease (HF/TIV, A/TIV, AHC/TIV, and CN/TIV) or enlargement (V/TIV) of Alzheimer disease values are presented in Table 2. In patients with Alzheimer disease, the decrease of the volume of the hippocampal formation and the amygdala was marked ($-30 \pm 3\%$ and $-37 \pm 2\%$, respectively)

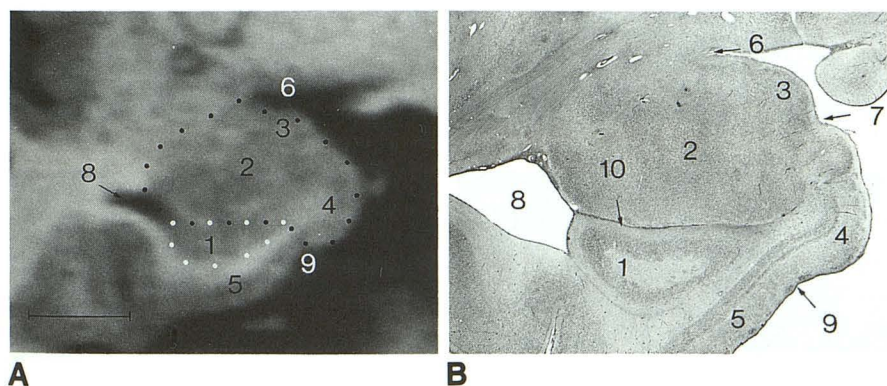


Fig. 6. Comparison of coronal oblique MR scan in one control brain (A) and histologic section (B) passing through the posterior part of the uncus. The hippocampal formation (white dots) and the amygdala (black dots) are outlined on the MR scan. 1 indicates Ammon's horn; 2, amygdala; 3, semilunar gyrus; 4, gyrus ambiens; 5, parahippocampal gyrus; 6, entorhinal sulcus; 7, sulcus semianularis; 8, uncus recess of the lateral ventricle; 9, uncus notch; and 10, alveus (scale bar, 1 cm).

(Fig 7) and significant in both structures ($P < .01$; Table 2). The mean TIV volumes were not significantly different in patients with Alzheimer disease and control subjects. The ventricles in Alzheimer patients were $25\% \pm 11\%$ larger than those of control subjects (Table 2), but the differ-

ence was not significant. The volume of the caudate nucleus was slightly but significantly smaller ($P = .03$; Table 2).

In the group with mild dementia ($MMSE \geq 21$, $n = 13$), the volume of the hippocampal formation and the amygdala was significantly less than

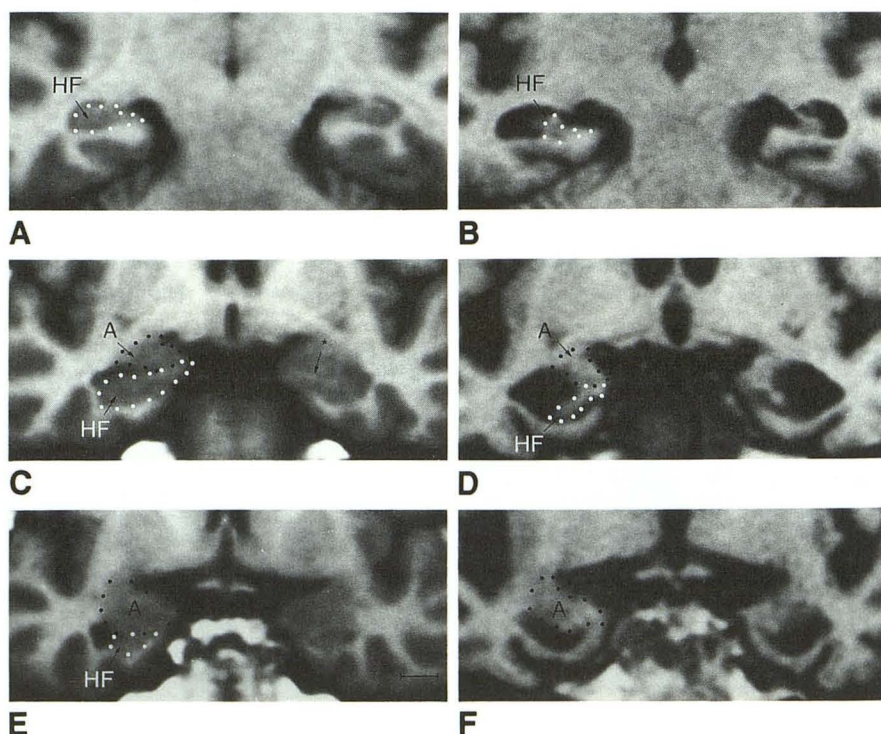
TABLE 2: Normalized volumes in patients with Alzheimer disease and control subjects

	Control (n = 8)	Alzheimer		
		Total (n = 18)	MMSE ≥ 21 (n = 13)	MMSE < 21 (n = 5)
V/TIV	21.42 $\pm$ 3.49	26.78 $\pm$ 2.31 (+25% $\pm$ 11%) $P = .21$	23.38 $\pm$ 2.18 (+9% $\pm$ 10%) $P = .62$	34.96 $\pm$ 4.23 (+63% $\pm$ 20%) $P = .03$
HF/TIV	2.38 $\pm$ 0.06	1.66 $\pm$ 0.08 (-30% $\pm$ 3%) $P < .01$	1.79 $\pm$ 0.08 (-25% $\pm$ 3%) $P < .01$	1.31 $\pm$ 0.07 (-45% $\pm$ 3%) $P < .01$
A/TIV	1.77 $\pm$ 0.09	1.12 $\pm$ 0.04 (-37% $\pm$ 2%) $P < .01$	1.13 $\pm$ 0.05 (-36% $\pm$ 3%) $P < .01$	1.07 $\pm$ 0.11 (-40% $\pm$ 6%) $P < .01$
AHC/TIV	4.14 $\pm$ 0.14	2.75 $\pm$ 0.10 (-34% $\pm$ 2%) $P < .01$	2.92 $\pm$ 0.10 (-29% $\pm$ 2%) $P < .01$	2.33 $\pm$ 0.11 (-44% $\pm$ 3%) $P < .01$
CN/TIV	2.71 $\pm$ 0.07	2.36 $\pm$ 0.09 (-13% $\pm$ 3%) $P = .09$	2.45 $\pm$ 0.12 (-9% $\pm$ 4%) $P = .12$	2.14 $\pm$ 0.08 (-21% $\pm$ 3%) $P < .01$

Note.—These are ratios expressing the volume of right plus left hippocampal formations (HF/TIV), amygdala (A/TIV), amygdalohippocampal complexes (AHC/TIV) and caudate nuclei (CN/TIV), divided by total intracranial volume ($\times 10^3$). V/TIV is a ratio of right plus left lateral ventricles plus third ventricle volumes on total intracranial volume ($\times 10^3$). Values in parentheses are the percent difference of measurements of patients with Alzheimer disease from those of controls (see Methods).

Fig. 7. Comparison of coronal oblique MR scans of the hippocampal formations and amygdala at corresponding levels in one control subject and one patient with Alzheimer disease.

A, Control MR scan at the level of the hippocampal body. B, Alzheimer MR scan at the level of the hippocampal body. C, Control MR scan at the level of the anterior commissure (asterisk indicates alveus). D, Alzheimer MR scan at the level of the anterior commissure. E, Control MR scan at the level of the amygdala. F, Alzheimer MR scan at the level of the amygdala. The hippocampal formation (white dots) and the amygdala (black dots) are outlined on the right. HF indicates hippocampal formation; and A, amygdala (scale bar, 1 cm).



that of control subjects ($-25\% \pm 3\%$ and $-36\% \pm 3\%$, respectively, $P < .01$; Table 2). Slightly and nonsignificantly smaller were the CN/TIV ($-9\% \pm 4\%$, $P = .12$) and ventricular enlargement (V/TIV, $+9\% \pm 10\%$, $P = .62$) (Table 2). In the group with moderate dementia ($10 < \text{MMSE} < 21$, $n = 5$), atrophy was more severe than in the mild stages of the disease for all nuclei studied (HF/TIV, $-45\% \pm 3\%$; A/TIV, $-40\% \pm 6\%$; CN/TIV, $-21\% \pm 3\%$; $P < .01$; Table 2). The ventricles were $63\% \pm 20\%$ larger than those of control subjects ($P = .03$; Table 2). Atrophy of the hippocampal formation and the amygdala, as expected, increased with the severity of the disease. Mean value of HF/TIV and A/TIV were 1.79 ± 0.08 and 1.13 ± 0.11 , respectively, for patients with Alzheimer disease in the mild dementia group, and 1.31 ± 0.07 and 1.06 ± 0.05 for patients in the moderate dementia group.

Plots of normalized volumes of patients with Alzheimer disease and control subjects for HF/TIV, A/TIV, and AHC/TIV are presented in Figure 8. Only two of the 18 patients with Alzheimer disease fell within the range of the control sub-

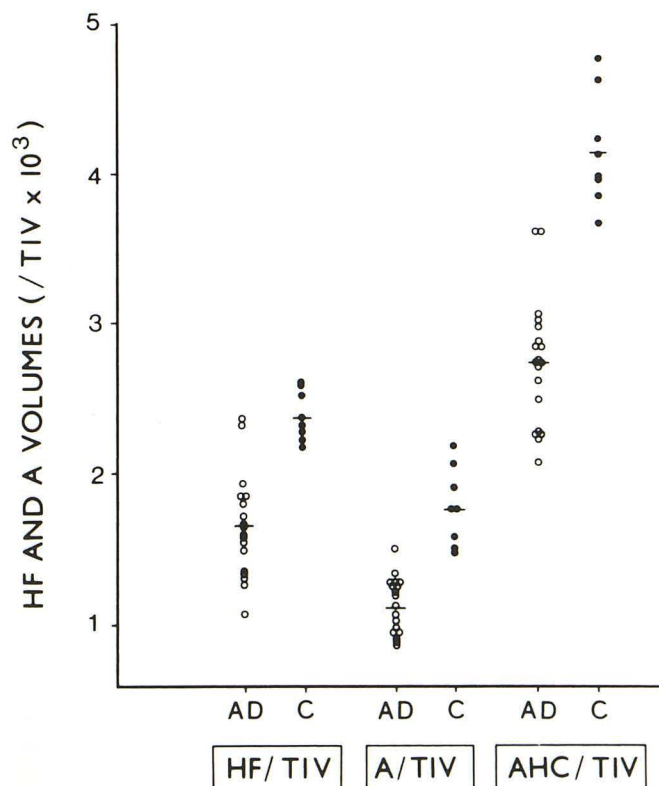


Fig. 8. Plots of normalized volumes of patients with Alzheimer disease and control subjects for HF/TIV, A/TIV, and AHC/TIV (open circle indicates Alzheimer; and filled circle, control subjects). AD indicates Alzheimer disease; and C, control subjects.

jects for HF/TIV, and one fell within the range of controls for A/TIV. These patients belonged to the mild dementia group. No patient fell within the range of the control subjects for AHC/TIV. Thus, 89% and 94% of the patients with Alzheimer disease were separated by HF/TIV and A/TIV, respectively, and all patients with Alzheimer disease were separated from control subjects by AHC/TIV. When the subpopulation of patients with mild dementia was considered separately, these values fell to 85% and 92%, respectively.

Regression analysis of normalized volumes on MMSE revealed a correlation between HF/TIV, V/TIV, and the MMSE ($r = .61$, $P < .01$, and $r = .59$, $P = .01$, respectively). No correlation was found between the volumes of the caudate nucleus or the amygdala and MMSE scores.

Discussion

The present data show that patients with Alzheimer disease in the mild to moderate stages of the disease have marked and significant atrophy of the hippocampal formation and the amygdala. This is in accordance with the severe histologic changes that have been repeatedly observed in the hippocampal formation and entorhinal cortex of patients with Alzheimer disease (3–6), and the 45% decrease in the volume of the amygdala, which has been reported in advanced stages of the disease (29). This figure is only 7% greater than the estimated atrophy of the amygdala in the present study for patients in the mild to moderate stages of the disease. The greatest reductions in size occurred in the lateral part (also called *pars lateralis* or *magnocellular compartments*) of the basal and accessory basal subnuclei (29). These nuclei were included in our measurements, but the various subnuclei of the amygdala could not be identified on MR scans.

Previous MR-based studies have reported atrophy of the hippocampal formation (15–17) and the amygdala (30). Our study extends these results. It shows that there is already atrophy of the hippocampal formation and the amygdala in the mild stages of the disease, in the absence of any change of the caudate nucleus and the ventricular volume. As expected, the atrophy of the hippocampal formation, amygdala, and caudate nucleus, and ventricular enlargement, increased with the severity of the disease (Table 2). These results indicate that degeneration of the hippocampal formation and the amygdala begins early

in the course of the disease. That these structures are specifically involved from the early stages of the disease, as shown in vivo in the present study, suggests that the neuropathologic process may begin in these areas (ie, hippocampal formation, entorhinal cortex, and amygdala) and then extend toward other cortical or subcortical areas (31).

The present study suggests that MR volume measurements of hippocampal atrophy may be a useful tool in differentiating patients with Alzheimer disease from elderly control subjects. These results agree with previous studies of hippocampal atrophy in Alzheimer disease, based on either CT (32–35) or MR scans (15–17). Although some of these studies, using volumetric or planimetric measurements of the hippocampal formation (15, 17), have reported complete separation of patients with Alzheimer disease from age-matched control subjects, the present study, with a larger sample size, found incomplete separation of the two groups. These results are in agreement with a recent report (16), suggesting that volumetric measurements of the hippocampal formation may not be as accurate in separating patients with Alzheimer disease from control subjects, as previously reported. Moreover, our experience suggests that simple visual inspection of the coronal MR images may not allow distinction of patients with Alzheimer disease from control subjects, as previously proposed (36), at least for patients in the mild stages of the disease. This fact highlights the significance of the volume measurements of the amygdala, which appeared more promising in separating patients from controls, because volume measurements of A/TIV led to correct diagnosis in 94% of patients with Alzheimer disease; however, the most powerful index was the volume of both hippocampal formation and amygdala (AHC/TIV), which more clearly separated patients with Alzheimer disease from control subjects, even in the mild stages of the disease. Thus, AHC/TIV may be the best volumetric index to assist the clinical diagnosis of Alzheimer disease.

A significant correlation was found between the MMSE scores, which assess a large spectrum of cognitive functions including memory, and both the V/TIV, in agreement with previous CT studies (23), and the HF/TIV. Such a correlation between cognitive impairment and hippocampal degeneration has been reported (15, 37), and emphasizes the role of the hippocampal damage in cognitive decline in patients with Alzheimer disease (9). This is in accordance with several

pieces of evidence implicating the hippocampal formation in memory processes in both humans (38–42) and primates (43). In contrast, no correlation has been found between the MMSE scores and A/TIV. The cognitive functions of the amygdala are still controversial (43, 44); this nucleus may not be part of the medial temporal lobe memory system (45). The amygdala is considered instead to contribute to the organization of affective behavior (46).

In summary, MR volume measurements of the hippocampal formation and the amygdala help to differentiate correctly patients in the mild stages of Alzheimer disease from age-matched control subjects. The lowest degree of overlap between patients with Alzheimer disease and control subjects occurred with measurements of the amygdala and the amygdalohippocampal complex, as compared with the hippocampal formation. Thus, this technique may be a useful tool for diagnosis of the mild stages of Alzheimer disease.

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