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Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions

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Summary. We studied the usefulness of measuring volumes of the hippocampus, amygdala and frontal lobes with coronal magnetic resonance imaging (MRI) scans in the diagnosis of early Alzheimer's disease (AD). We examined 32 patients diagnosed according to the NINCDS-ADRDA criteria of probable AD and 16 age-matched healthy cognitively normal controls. The AD patients had mild dementia with a mean score of 22.8 in the Mini-Mental Status Examination (MMSE). We used a 1.5 T magnetic resonance imager and normalized the volumes for brain area. The AD patients had significantly smaller volumes of the right and the left hippocampus (−38%) (ANOVA, $p < 0.0001$) and the left frontal lobe (−16%, $p < 0.05$) compared to controls. The reductions in volumes of the right frontal lobe (−13%), the right amygdala (−14%) or the left amygdala (−18%) were not statistically significant. In the discriminant function analysis which included the volumes of the hippocampus, amygdala, and the frontal lobes and age, the volumes of the left and right hippocampus, the left and right frontal lobe, and the right amygdala entered the model and we could correctly classify 92% of the subjects into AD and control groups (Chi-square 42.6, df 5, $p < 0.0001$). By using the volumes of the hippocampus, the frontal lobes or the amygdala on their alone, the correct classification was achieved in 88%, 65% and 58% of the subjects, respectively. In addition, in AD patients the volumes of the left hippocampus correlated significantly with the MMSE score and with immediate and delayed verbal memory; the smaller the volume the more impaired was their performance. Our data indicate that measurements of volumes of the hippocampus might be useful in diagnosis of early AD.

Keywords: Alzheimer's disease, amygdala, dementia, frontal lobe, hippocampus, magnetic resonance imaging, memory.

Introduction

There are problems in the clinical diagnosis of Alzheimer's disease (AD), an accuracy of between 80–90% is the best one can achieve (Sulkava et al., 1983; McKhann et al., 1984). Thus the definitive diagnosis can be obtained only by means of biopsy or autopsy (McKhann et al., 1984). Imaging methods, computed tomography (CT) and magnetic resonance imaging (MRI), are an integral part of the diagnostic assessment of patients with suspected dementia and help to detect specific central nervous system causes of dementia such as brain tumor, vascular lesions, normal pressure hydrocephalus, and chronic subdural haematoma. The value of linear, planimetric and volumetric measurements of various regions of interest on CT scans have been under scrutiny in attempts to separate AD patients from elderly controls (DeCarli et al., 1990). Recently, similar approaches have been applied with MRI scans. MRI studies, though varying to some extent, have shown interesting and promising results in providing a reliable, non-invasive method for the diagnosis of AD. Therefore, we wanted to confirm some of the previous results and seek a reliable means of improving the accuracy of the diagnosis of AD by volumetric measurements using MRI.

Previous studies applying CT have shown that volumetric measurements were able to classify up to 90% of AD patients and control subjects (DeCarli et al., 1990). Functional techniques, such as measuring cerebral glucose metabolism and regional cerebral blood flow with positron emission tomography and single-photon emission computed tomography (SPECT) have also been used for the diagnosis of AD (Haxby et al., 1986; Pearlson et al., 1992). SPECT measurements alone were able to differentiate 88% of the AD-patients from the controls. By combining SPECT with MRI the results have been even better (Pearlson et al., 1992). Magnetic resonance spectroscopy, a method recently introduced to study metabolism of the brain, has also been utilized in examining AD patients (Bottomley et al., 1992; Klunk et al., 1992; Longo et al., 1993). Furthermore, measurement of magnetic resonance T_2 relaxation time in the hippocampus has shown promising results with the prolongation of the T_2 relaxation time correlating with the severity of AD symptoms (Kirsch et al., 1993).

Earlier studies on the volumetric MRI-diagnosis of AD and also on the normal variations and the changes in aging have focused on the temporal lobe as a whole, or individually on the temporal neocortex, the superior temporal gyrus, the hippocampal formation, the uncus, the entorhinal cortex, the parahippocampal gyrus, and the amygdala. Ventricular spaces of interest have been the ventricles, the temporal horns, the interuncal distance, the temporal sulci and the Sylvian fissures, as well as the choroidal fissure, the subarachnoid space and the cerebrospinal fluid. Moreover, several extratemporal regions have been measured, such as the brain parenchyma, the frontal cortex, the parietal cortex, the corpus callosum, the basal forebrain, and the basal ganglia; striatum, nucleus caudatus and nucleus lenticularis (Seab et al., 1988; Krishnan et al., 1990; Bronen and Cheung, 1991a; Dahlbeck et al., 1991;

Jernigan et al., 1991; Kesslak et al., 1991a; Pearlson et al., 1992; Murphy et al., 1992; Cuénod et al., 1993; Doraiswamy et al., 1993; Erkinjuntti et al., 1993; Killiany et al., 1993).

In aging, MRI studies have detected decreased volumes of the anterior diencephalic structures, of the grey matter of most cortical regions, especially of association cortices and mesial temporal lobe structures (Jernigan et al., 1991), and of the caudate nucleus (Krishnan et al., 1990; Jernigan et al., 1991). The age-related changes in the white matter are also manifest as prolonged T_2-values (Jernigan et al., 1991). The volumes of the lateral ventricles have been reported to increase by 3.2% per year (Coffey et al., 1992). There are also normal variations in the temporal lobe including notching of the uncus and asymmetry of the temporal horns. Mild asymmetry of the hippocampal head and mild enlargement of the right temporal lobe were not uncommon. Other variations were subtle asymmetry of the white matter between the hippocampus and the collateral sulcus, atypical sulci and Sylvian fissure dilatation (Bronen and Cheung, 1991a).

Despite the intense effort to define an accurate variable, a structure, a combination of structures or even a combination of structural and functional measurements to reveal early AD, no uniformity or simple answer has been achieved. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has tried to develop procedures for standardized imaging and reporting MRI findings but no satisfactory interrater agreement for interpreting MRI findings in elderly subjects was found. Acceptable intraclass correlations in a group of 14 neuroradiologist were obtained only in the ratings of the lateral and third ventricles and the temporal horn. What is needed are more objective and reproducible procedures for interpretation of neuroimaging findings of AD (Davis et al., 1992).

We chose the hippocampus and the amygdala as well as a neocortical region, the frontal lobe, as regions of interest. Memory loss is the most common early symptom in AD. The hippocampus, which is closely associated with memory processing, is known to be vulnerable to damage in the early stage of AD (Hyman et al., 1984). The purpose of our study was to assess the usefulness of MRI volume measurements in the diagnosis of early AD. To this end we measured the volumes of the hippocampus, the amygdala and the frontal lobes using thin slices to obtain as precise information as possible. To test the value of volume measurements as a tool to separate AD patients from controls, we applied a discriminant function analysis. We also correlated the volumes of these brain regions with the patients' performance on tests assessing verbal and visual memory as well as executive functions.

Material and methods

Patients and controls

We examined 32 patients fulfilling the NINCDS-ADRDA criteria of probable AD (McKhann et al., 1984) and 16 age- and sex-matched controls. The clinical characteristics of the subjects are presented in Table 1. The ethics committee of the University

Table 1. Clinical characteristics of controls and Alzheimer patients (AD)

	Controls	AD	ANOVA F
Number	16	32	
Women/men	10/6	15/17	
Mean age, years	70 ± 5	69 ± 8	NS
Age at onset, years	–	66 ± 9	
Duration, months	–	29 ± 17	
Mini-Mental Status	28.6 ± 1.4	22.8 ± 3.7	36.4**
Brief Cognitive Rating Scale	–	2.9 ± 0.8	
Education, years	11.8 ± 3.0	8.5 ± 4.1	8.1*

Results are mean ± S.D.
ANOVA; *$p < 0.01$, **$p < 0.0001$, *NS* not significant

Hospital and University of Kuopio approved the study. All subjects gave their informed consent for participation in the study following the explanation of the study protocol.

The AD patients underwent the following examinations: general physical and clinical neurological examination; assessment of clinical severity using Mini-Mental Status Examination (MMSE) (Folstein et al., 1975) and Brief Cognitive Rating Scale (BCRS) (Reisberg et al., 1983); assessment of extrapyramidal signs using Webster Parkinson's Disease scale (Webster, 1968); assessment of depressive signs by the Hamilton scale (Hamilton, 1960); an extensive battery of laboratory tests to exclude secondary causes of dementia; neuropsychological tests; EEG and event-related potentials; SPECT-scan; and magnetic resonance imaging of the brain. All patients scored less than four in the modified ischemic scale (Rosen et al., 1980).

The controls have been described in detail elsewhere (Soininen et al., 1994). Their investigation also included clinical neurological examination, neuropsychological testing, EEG, event-related evoked potentials, and MRI.

Neuropsychological tests

Verbal memory was examined with the list learning test using shopping items (Helkala et al., 1988). A "yes" or "no" recognition of the words in the list was asked after a 30-minute delay filled with other psychometric tests. We also used the story recall test with the Boston approach (Millber et al., 1986). The recall of the story was tested immediately and after a 30-minute delay. Visual memory was examined with Heaton Visual Reproduction Test (Russel, 1975). The recall of the figures was tested both immediately and after a 30-minute delay.

To assess executive functions we used Nelson's version of the Wisconsin Card Sorting Test (Nelson, 1976), Trail-Making test A and B (Reitan, 1958), and Verbal Fluency (Borkowski et al., 1967). The maximum time of 150 seconds for Trail-Making A and 300 seconds of Trail Making B was allowed. If the test was not completed *in the time allowed*, the missing letters or numbers were scored as omissions. In the Verbal Fluency Test the subject was asked to produce as many words as they could beginning with letters P, A and S in one minute for each letter. The score was the number of words correctly named. Furthermore, we examined verbal functions with the Boston Naming Test (Kaplan et al., 1983), visuospatial functions with copy a cube test, clock setting test and the Block Design subtest of Wechsler Adult Intelligence scale (Goodglass and Kaplan, 1972; Wechsler, 1981), and praxic functions of the hand using Luria's method (Helkala et al., 1988) (data not shown).

MRI imaging technique

The subjects were scanned with a 1.5 T Magnetom (Siemens, Erlangen) using the standard head coil and a tilted coronal 3D gradient echo sequence (MP-RAGE: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 × 192, 1 acquisition). This resulted in 128 T1-weighted partitions with slice thickness of 1.5–1.8 mm oriented at a right angle to the long axis of the hippocampus. The radiologist who analyzed the MRIs was blinded to the subject's clinical diagnosis.

We used standard anatomical atlases of the human brain (Duvernoy, 1988; DeArmond et al., 1989) with some adjustment from previous articles (Naidich et al., 1987; Bronen and Cheung, 1991b; Tien et al., 1992; Watson et al., 1992) as guidelines to determine the boundaries of the amygdala and the hippocampus in oblique coronal MRI sections. The method has been reported previously in detail (Soininen et al., 1994). The boundaries of the region of interest were outlined by a trackball driven cursor and the number of voxels within the region was calculated by using an in-house developed program for standard work console. The outlining of the boundaries always proceeded from anterior to posterior.

The outlines of the amygdala included the deep nuclei of the amygdala, the superficial nuclei of the amygdala, and the remaining nuclei of the amygdala. At the most rostral sections of the amygdala, we outlined only the deep amygdaloid nuclei in the MRI image to avoid any overestimation of the amygdaloid volume due to inclusion of the piriform cortex. The hippocampus included the dentate gyrus, the hippocampus proper and the subicular complex. The uncal portion of the rostral hippocampus that is located ventral to the caudal amygdala was included into the hippocampus. The caudal end of the hippocampus was determined from the section, in which the fornices were still detectable in their full length.

To determine the volumes of the frontal lobes, the gyri were manually outlined on every third slice. Thus, due to thin slices, the measurement was done at an interval of 5 mm. The most anterior of the slices was the one with clearly visible gyri. On the most posterior slices, a straight line was drawn from the bottom of the lateral fissure to the choroidal fissure in order to separate the temporal lobe from the frontal lobe. From the bottom of the choroidal fissure a line was drawn above the optic tract to the midline and then a line was drawn vertically to the interhemispheric cerebral fissure. The most caudal slice included in the measurement was the one in which the anterior commissure was present. The volume of the lateral ventricles was also measured and consequently subtracted from the volume of the slice. The volume of each slice was multiplied by three and thereafter, the slice volumes were summed.

In the statistical analysis, we used volumes of the region of interest normalized for the brain area. Normalization was done by dividing the volumes of the hippocampus, amygdala, or the frontal lobe by brain area. To obtain brain area, we measured the area of both hemispheres in a MR image taken at the level of the anterior commissure. The normalization yielded ratios: volume of the region of interest/brain area. We used normalized values in all statistical analyses.

The intrarater agreement of this method has been reported earlier (Soininen et al., 1994). The interrater reproducibility between two raters was tested in 16 subjects. The differences between the volumes obtained by two raters compared to the mean of these two measurements were 4.1% for the right hippocompus and 1.6% for the left hippocampus, 8.7% for the right amygdala and 3.7% for the left amygdala.

Statistical analysis

The data were analyzed by utilizing SPSS-PC+ V.4.1 software (SPSS Inc., Chicago, IL). In all statistical analyses of the volumetric data, we used volumes normalized for brain area. Analysis of variance (ANOVA) was used to compare the means between the study groups. Correlations were calculated by using *Pearson's correlation two-tailed test.* To test the accuracy of volume measurements to distinguish AD patients from controls we used

stepwise discriminant function analysis (Wilk's method). The results are expressed as mean ± standard deviation (S.D.). The level of statistical significance of differences is $p < 0.05$.

Results

The AD patients and controls did not differ significantly in age or sex (Table 1). The controls had a longer education than the AD patients [ANOVA, $F(1,46) = 8.1$, $p < 0.01$]. As expected, MMSE scores were higher in controls than in AD patients [$F(1,46) = 36.4$, $p < 0.0001$].

Volumetric measurements

Table 2 presents the mean volumes of the regions of interest and Fig. 1 A–C demonstrate distribution of ratios of these volumes and the brain area. AD patients had significantly smaller volumes of both hippocampi (ANOVA, $p < 0.0001$) and the left frontal lobe compared to controls (ANOVA, $p < 0.05$). The volumes of the right frontal lobe and the amygdala did not differ significantly between the AD and control groups.

Discriminant function analysis

We tested the value of volume measurements to differentiate AD patients from controls in four stepwise discriminant function analyses. In the first analysis, we included volumes of the hippocampus, amygdala, and frontal lobes as well as age. The volumes of the left and right hippocampus, the left and right frontal lobe, and the right amygdala entered the model and the analysis yielded a correct classification in 94% of AD patients and 88% of controls (Chi-square = 42.6, df 5, Wilks' lambda 0.38, $p < 0.0001$) (Table 3). Table 4 shows the standardized canonical discriminant function coefficients for the variables that entered the model. The coefficients are positive for the left and right hippocampus and the left frontal lobe indicating that the controls have larger volumes. The coefficients are negative for the right frontal lobe and the right amygdala that may be partly explained by intercorrelation of the volumes. Wilks' lambda values show that the volume of the left hippo-

Table 2. Mean volumes (cm^3) for controls and patients with Alzheimer's disease (AD)

	Controls N = 16	AD N = 32	Decrease %	ANOVA F
Right hippocampus	3.714 ± 0.446	2.303 ± 0.591	38.0	43.1**
Left hippocampus	3.353 ± 0.511	2.084 ± 0.545	37.9	43.2**
Right amygdala	1.690 ± 0.239	1.460 ± 0.501	13.6	0.60
Left amygdala	1.851 ± 0.232	1.514 ± 0.458	18.2	2.97
Right frontal lobe	120.0 ± 19.2	104.4 ± 16.3	13.0	1.6
Left frontal lobe	118.4 ± 19.5	99.1 ± 15.9	16.3	5.3*

Results are mean ± S.D. The volumes were normalized for brain area prior to the statistical analysis. ANOVA; *$p < 0.05$, **$p < 0.0001$

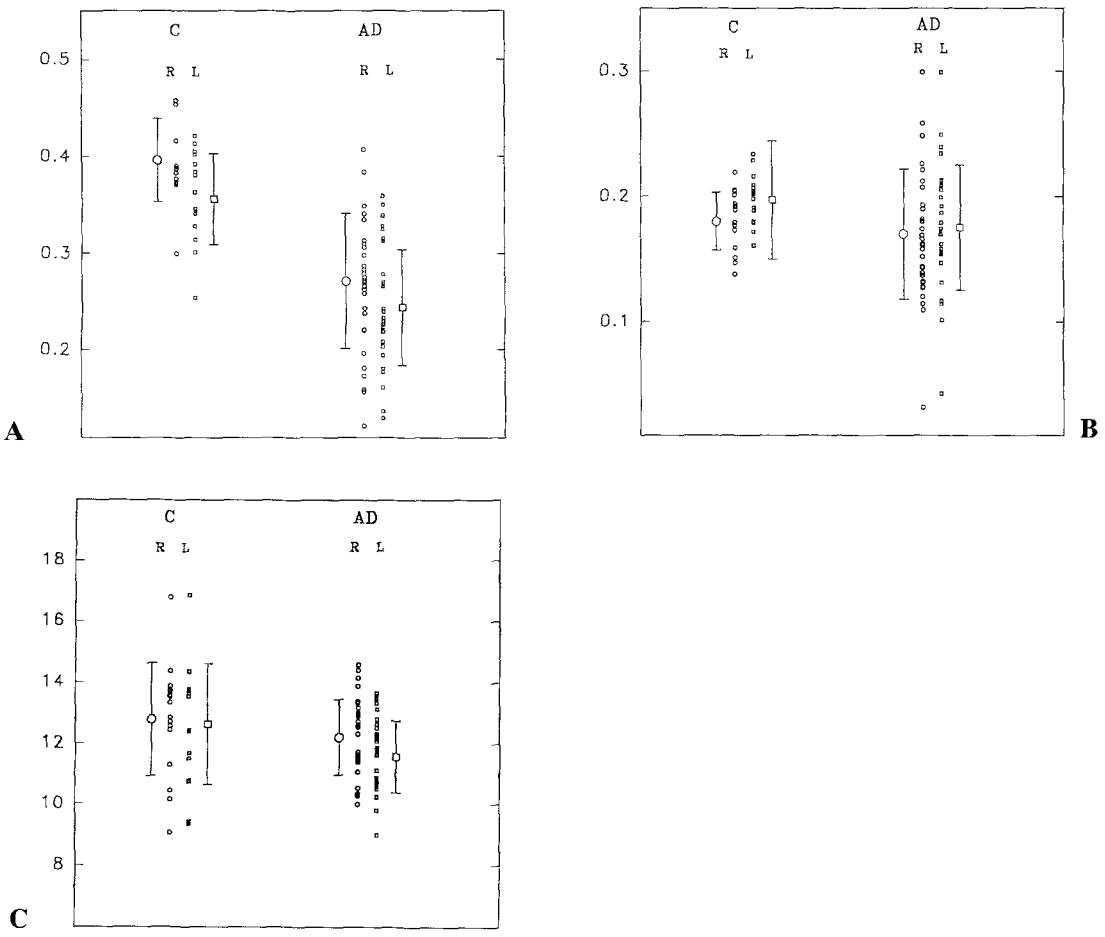

Fig. 1. Scattergram of ratios calculated by dividing the volume of the hippocampus (**A**), the amygdala (**B**), and the frontal lobe (**C**) by brain area measured on MRI scan at the level of the anterior commissure for controls (C) and Alzheimer patients (AD). Abbreviations: *R* right; *L* left. The bars indicate mean ± S.D.

campus explains 48% of the variance between AD patients and controls. The contributions of the other volumes is less (the right hippocampus, 4%; the left frontal lobe, 4%; the right frontal lobe, 5%; and the right amygdala, 1%) resulting in 62% explanation of the variance for this model.

The second analysis included the volumes of the right and left hippocampus and both volumes entered the model and resulted in a correct classification in 94% of AD patients and 84% of controls (Chi-square = 33.1, df 2, Wilks' lambda 0.48, $p < 0.0001$). If one included only the volume of the left hippocampus, a sensitivity of 78% and a specificity of 94% was achieved.

In the third analysis comprising the volumes of the frontal lobes, only the volume of the left frontal lobe entered the model and the correct classification was achieved in 66% of AD patients and 63% of controls (Chi-square 5.0, df 1, Wilks' lambda 0.90, $p = 0.026$).

In the fourth analysis including the volumes of the amygdala, the model resulted in a correct classification in only 69% of AD patients and 53% of

Table 3. Classification of controls and Alzheimer patients using discriminant function analysis including volumes of the hippocampus, amygdala, and frontal lobes

	Sensitivity %	Specificity %	Overall correct classification %
Hippocampus	84.4 (27/32)	93.8 (15/16)	87.5
Frontal lobe	65.6 (21/32)	62.5 (10/16)	64.6
Amygdala	53.1 (17/32)	68.8 (11/16)	58.3
Combined	93.8 (30/32)	87.5 (14/16)	91.7

Number of subjects is in parentheses. The combined analysis included all volumes measured as well as age; the volumes of the left and right hippocampus, the left and right frontal lobe, and the right amygdala entered the model (Chi-square = 42.6, df 5, Wilks' lambda 0.38 $p < 0.0001$)

Table 4. Discriminant function analysis between Alzheimer patients and controls including volumes of the hippocampus, amygdala, and frontal lobes, and age

Step	Volume	Wilks' lambda	Explains % of variance	Standardized canonical discriminant function coefficient
1	Left hippocampus	0.52	48	0.91
2	Right hippocampus	0.48	52	0.29
3	Left frontal cortex	0.44	56	0.81
4	Right frontal cortex	0.39	61	−0.65
5	Right amygdala	0.38	62	−0.27

The volumes of the left and right hippocampus, the left and right frontal lobe, and the right amygdala entered the model (Chi-square = 42.6, df 5, Wilks' lambda 0.38 $p < 0.0001$)

controls (Chi-square = 2.9, df 1, Wilks' lambda 0.94, $p = 0.09$). Thus, the volumes of the right and left hippocampus and the left frontal lobe were the best parameters in differentiating AD patients from controls.

Memory and executive functions

As expected AD patients showed significant impairment on tests assessing verbal and visual memory and on executive functions (ANOVA; $p < 0.0001$) compared to controls (Table 5). The significances did not change when education was included as a covariate in the analysis.

Correlations of MRI volumetric measures

The volumes of the hippocampus, the amygdala or frontal lobes did not correlate with age or education in AD patients or controls. In AD, there was no significant relationship between volumetric measures and age of onset or duration of the disease. In the AD group, the volume of left hippocampus significantly correlated with MMSE ($r = 0.42$, $p = 0.019$), immediate story recall ($r = 0.39$, $p = 0.029$) and delayed story recall ($r = 0.50$, $p = 0.003$).

Table 5. Mean scores of tests assessing memory and executive functions for controls and Alzheimer patients

	Control N = 16	Alzheimer N = 32	ANOVA F
Immediate memory			
List learning	44.6 ± 6.2	19.5 ± 9.5	91.6
Visual reproduction	12.1 ± 2.7	4.8 ± 2.5	86.2
Story recall	–	8.2 ± 4.7	–
Delayed memory			
List learning	10.0 ± 0	5.9 ± 3.5	21.7
Visual reproduction	11.8 ± 3.6	1.4 ± 2.0	166.7
Story recall	–	5.8 ± 3.5	–
Executive functions			
Trail Making A	46.2 ± 19.6	108.0 ± 40.0	33.9
Trail Making B	196.1 ± 70.8	276.5 ± 55.3	18.7
Wisconsin Card Sorting	4.4 ± 2.1	1.1 ± 1.4	42.1
Verbal fluency	55.6 ± 18.2	21.6 ± 13.1	55.1

Results are expressed as mean ± S.D. ANOVA shows that controls differ from Alzheimer patients in all test scores, $p < 0.0001$

With respect to frontal lobe functions, the volume of left frontal lobe correlated significantly with Trail-Making A ($r = -0.44$, $p = 0.013$), the longer time spent in the test the smaller the volume of the left frontal lobe. The number of errors in Trail-Making A also correlated with the volume of the right frontal lobe ($r - 0.44$, $p = 0.014$). No other significant correlations were found between MRI volumetric measures and cognitive functions.

Discussion

This study focused on measurement of volumes of the hippocampus, amygdala and frontal lobes. Our purpose was to search for a reliable means for diagnosing early AD using MRI. In order to optimize the volumetric method we used a program developed in-house to calculate the volumes, measurement of the structures of interest as whole, and thin slices optimally oriented for mesial temporal structures, which we believe, provides excellent accuracy and reproducibility. The use of stereology is another method for measuring volumes of specific structures by MRI (Krishnan et al., 1990). The computed MRI volumetry, however, is more accurate and reduces stages in which variability can be introduced (Kesslak et al., 1991b).

We found a 38% decrease in the volume of the right and left hippocampus in AD patients compared to control. Our main finding was the 92% accuracy obtained in differentiating the AD group from the controls by discriminant function analysis using the hippocampal, frontal lobe, and amygdaloid volumes. The volumes of the hippocampi and the left frontal lobe were significantly smaller in the AD group compared to controls and those were the best discriminators in the discriminant function analysis. The diminished volumes of the left hippocampus correlated with the decline of MMSE scores and

impaired verbal memory. Impaired performance on the Trail-Making test, which is a test considered to assess frontal lobe functions, was associated with decreased volumes of the frontal lobes.

In a previous study, the hippocampus measured from a single slice did not differ in size between the early AD group and controls (Cuénod et al., 1993). In agreement with this, Erkinjuntti and coworkers measured hippocampal area at the level of the hippocampal head and were able to differentiate only 41% of the early AD group from the controls (Erkinjuntti et al., 1993). Thus, measurements of the hippocampal area from one slice have not been as successful in differentiating the AD group from controls as volumetric results, which have yielded greater accuracy. For example, Seab and coworkers detected no overlap in hippocampal volumes among 10 early AD patients and 7 controls (Seab et al., 1988). Kesslak et al. found a reduction of 48.8% in the hippocampal volume in the early AD group (8) compared to age-matched controls (7) (Kesslak et al., 1991a). In another study, hippocampal volumes in 85% of 20 early AD patients fell below those of 22 controls (Jack et al., 1992). Killiany and coworkers could correctly identify 100% of the controls and the early AD group using a discriminant function analysis including a combination of volumes of hippocampus and temporal horn of the lateral ventricle (Killiany et al., 1993).

In line with our findings, an in vitro 7 T MR microscopy study of the hippocampus in AD indicated that the cross-sectional area of the hippocampus was decreased by 31% compared to the control group (Huesgen et al., 1993). This atrophy was also highly correlated with tangle counts within the hippocampus, but not with plaque counts. In addition, a recent study using stereological techniques to compare the regional pattern of neuronal cell loss in the hippocampus showed that AD patients have 25% neuronal loss in the hilus, 68% loss in the CA1 region, and 47% loss in the subiculum greater than those found in normal aging (West et al., 1994).

Studies in non-human primates have suggested that the hippocampus as well as the adjacent neocortex, are necessary for acquisition, temporary storage and retrieval of explicit memory (Zola-Morgan et al., 1982). In normal subjects, a study measuring regional cerebral blood flow using the $H_2{}^{15}O$ method showed that the right hippocampal region is activated in association with memory function (Squire et al., 1992). In epileptic patients, *a* focus in the right hippocampus led to impairment on visual memory tests whereas left hippocampal foci were associated with impairment on verbal memory tests (Miller et al., 1993). In agreement with earlier human data which have emphasized the importance of the hippocampus for associative memory, our study also showed a significant association between the shrinkage of the left hippocampus and impairment of verbal memory in AD patients.

Taken together, previous studies and our results suggest that the volume of the hippocampus is a sensitive measure of AD already in the early course of the disease. By measuring only the volume of the left hippocampus, the AD patients were separated from controls with a sensitivity of 78% and a specificity of 94%. Hippocampal atrophy, however, is not specific nor exclusive to AD. The volume of hippocampus has been shown to decrease for example in epilepsy, schizophrenia, and circumscribed amnesia (Press et al., 1989; Jack et

al., 1990; Suddath et al., 1990). Data on hippocampal volumes in patients with other dementing disorders, such as vascular dementia and Parkinson dementia, are not available. However, in many dementing illnesses, the clinical symptoms and other changes on CT or MRI scans, such as ischemic lesions, are useful diagnostic aids.

In the present study the volumes of the right amygdala (−14% of control) or the left amygdala (−18%) were not significantly reduced in AD patients. This finding agrees with some (Killiany et al., 1993) but not all previous studies (Scott et al., 1991; Pearlson et al., 1992; Cuénod et al., 1993). Cuénod et al. measured volumes of amygdala in 11 patients with early AD and 6 controls and found a 43.5% difference in the volume of the amygdala with only one overlap between the AD and the control group (Cuénod et al., 1993). Killiany et al. did not detect any significant difference in the volumes of the amygdala between 8 early AD patients and 7 controls (Killiany et al., 1993). In another study, the combined volumes of the left amygdala and the left entorhinal cortex identified 67% of 15 patients with moderately severe AD and 100% of 16 controls. Only two levels of the amygdala were measured (Pearlson et al., 1992). In an autopsy study, Scott et al. found in patients with advanced AD that the amygdalar nuclei showed significant atrophy except for the paralaminar portion of basal nucleus compared to age-matched controls. The magnocellular regions of the amygdala showed proportionally greater size reductions than other areas (Scott et al., 1991).

Even though there are detailed descriptions of MRI anatomy of amygdala (Naidich et al., 1987; Bronen and Cheung, 1991b; Jack et al., 1992; Tien et al., 1992), the measurement of the amygdala has proved to be complicated. In the study of Cuénod et al., for example, the interrater variability was 13% (Cuénod et al., 1993). Separating the anterior amygdala and the amygdala from uncus seem to be the most difficult task in the measurement and is responsible for much of the variability in the measurements (Davis et al., 1992; Jack et al., 1992; Pearlson et al., 1992; Tien et al., 1992; Cuénod et al., 1993; Killiany et al., 1993). Our radiologists also agreed that the anterior amygdala was the most difficult of the structures which they had to measure. In spite of the more complicated anatomy and shape of the hippocampus, it was easier and could be measured more exactly than the amygdala (Jack et al., 1992; Tien et al., 1992). By using imaging planes oriented perpendicular to the hippocampus, together with proper imaging parametres (heavily T_1-weighted/fast spin echo sequence) that maximize gray/white matter contrast, the entire hippocampus can be reliably measured (Press et al., 1989; Bronen and Cheung, 1991b; Tien et al., 1992). This view is also supported by our better interrater reliability data for the hippocampus than for the amygdala. In addition to the differences and difficulties in methodology, the discrepancy in volumes of the amygdala in distinct studies is probably due to differences in the clinical severity of the AD patients studied.

The good results in separating the AD group and the controls in our study suggest that such volumetric measurements might be useful in the diagnosis of early AD. The most efficient discriminating measures were the volumes of the right and left hippocampus and the left frontal lobe. Nonetheless, 100% accuracy in diagnosis remains elusive.

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