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Comparative MR Analysis of the Entorhinal Cortex and Hippocampus in Diagnosing Alzheimer Disease

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BACKGROUND AND PURPOSE: **Our purpose was to use volumetric MR imaging to compare the extent of atrophy and discriminative ability of the volumes of two temporal lobe structures, the entorhinal cortex and the hippocampus, between patients with Alzheimer disease and control subjects.**

METHODS: **The study group consisted of 30 patients with probable Alzheimer disease diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and 32 healthy control subjects. The MR volumes of the entorhinal cortex and the hippocampus were used for the discriminant function and receiver operator characteristic analysis as well as multivariate analysis of variance for repeated measures to compare their discriminative power.**

RESULTS: **Compared with control subjects, patients with Alzheimer disease had significantly smaller volumes of the entorhinal cortex and the hippocampus on both sides. Both the receiver operator characteristic and the discriminant function analyses using both volumes classified control subjects and Alzheimer patients with a high degree of accuracy (approximately 90%). Significant group × region interaction favoring hippocampal volumetry was determined by multivariate analysis of variance.**

CONCLUSION: **The volumetric measurements of both the entorhinal cortex and hippocampus have comparably high discriminative power in diagnosing Alzheimer disease. In clinical practice, hippocampal volumetry may be more feasible, because the method is easier to use and has less variability.**

Findings of several MR imaging studies have established that volumetry of the hippocampus is useful in assisting the clinical diagnosis of Alzheimer disease (1–8). However, results have varied across the studies; while some authors have reported no overlap between patients with Alzheimer disease and control subjects (1, 4, 5), others have found some overlap between the two groups (2, 6, 7). Measuring the volume of the entorhinal cortex, which may show neuropathologic changes of Alzheimer disease earlier than the hippocampus (9, 10), might offer another approach and improve diagnostic accuracy in the mildest phases of the disease. Recently, histology-based criteria for measuring the entorhinal cortex on MR images has been introduced (11), and the sensitivity of the entorhinal cortex alone in diagnosing Alzheimer disease has also been reported (3, 12). However, no comparison has been made between the discriminatory power of volumetry of the hippocampus and the entorhinal cortex to distinguish Alzheimer patients from control subjects. To compare the accuracies of these two volumetric measurements in distinguishing Alzheimer patients from cognitively normal control subjects, we used discriminant function analysis and the receiver operating characteristic (ROC) method as well as multivariate analysis of variance (MANOVA) for repeated measures. An additional aim of the study was to compare the extent of atrophy of the entorhinal cortex with that observed in the hippocampus.

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From the Department of Neuroscience and Neurology (K.J., M.P.L., H.S.), University of Kuopio; and the Departments of Neurology (H.S.) and Radiology (M.P.L., K.P.), Kuopio University Hospital, Kuopio, Finland.

Address reprint requests to Hilkka Soininen, MD, PhD, Department of Neurology, Bldg. 5, Kuopio University Hospital, P.O. Box 1777, FIN-70 211 Kuopio, Finland.

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Methods

Subjects

The sample consisted of 30 patients (15 women and 15 men) with recently diagnosed Alzheimer disease. The patients underwent a complete physical and neurologic examination, an

extensive battery of laboratory tests to exclude secondary causes of dementia, neuropsychological tests, electroencephalography, event-related potentials, single-photon emission CT, and MR imaging of the brain. The ischemic score for all subjects was less than 4 in the modified ischemic scale (13). All patients fulfilled the criteria for probable Alzheimer disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (14). The control subjects (20 women and 12 men) were randomly selected from participants in a population-based study (15). They were investigated similarly to the patients with Alzheimer disease and were found to be healthy, with normal cognitive functions as evidenced by neuropsychological testing. The local ethics committee approved the study. Each subject provided his or her informed consent for participation in the study after an explanation of the investigation protocol.

The mean age of the control subjects was 72 ± 4 years (range, 64 to 79 years) and that of the patients was 70 ± 8.5 years (range, 50 to 83 years). The groups did not differ significantly in age (one-way analysis of variance [ANOVA]; $F = 1.04$, $P = .3122$) or sex ($\chi^2 = 1.03$, $df = 1$, $P = .3096$). Control subjects had a higher level of education (mean, 9.6 ± 3.6 years; range, 4 to 16 years) than patients with Alzheimer disease (mean, 6.5 ± 1.8 years; range, 4 to 12 years) (one-way ANOVA; $F = 18.57$, $P = .0001$). In this age group, basic elementary school education was 6 years, and it is possible that some individuals had completed even less than 6 years of formal education, especially in rural areas. The clinical severity of Alzheimer disease was assessed by the Mini-Mental State Examination (16) and the Clinical Dementia Rating scale (17). The patients were in mild to moderate stages of the disease; 14 patients scored 1 and 16 patients scored 2 on the Clinical Dementia Rating scale. The average score in the Mini-Mental State Examination was 20.7 ± 3.7 (range, 14 to 28) in the group with Alzheimer disease and 28.3 ± 1.4 (range, 25 to 30) in the control group (one-way ANOVA; $F = 116.31$, $P = .0001$).

MR Technique

MR images were acquired with a 1.5-T MR unit using a standard head coil and a tilted coronal 3D magnetization prepared rapid gradient-echo sequence with the following parameters: TR/TE/excitations = 10/4/1, TI = 250, flip angle = 12°, field of view = 250 mm, and matrix = 256 × 192), resulting in 2-mm-thick sections on contiguous T1-weighted images. The regions were manually traced by a trackball-driven cursor on successive MR images, and the volume was calculated by software developed in-house for a standard work console.

Volumetric Assessment

Entorhinal Cortex—The entorhinal cortex (Brodmann's area 28) is a gray matter structure beginning approximately at the level of the limen insulae and extending caudally to the level of the gyrus intralimbicus. It is bounded superiorly by the amygdala and the hippocampus and inferiorly by the collateral sulcus. Laterally and superiorly, the border of the entorhinal cortex is defined by the white matter of the parahippocampal gyrus and laterally also by the perirhinal cortex. As anatomic landmarks for the measurements of the entorhinal cortex on MR images were defined perpendicular to the plane connecting the anterior and posterior commissures (11), the images were tilted coronally to this plane and were traced from 2-mm-thick contiguous sections.

Hippocampus—The hippocampi were measured as described earlier; the rostral end of the hippocampus when it first appeared below the amygdala was the starting point. The caudal end of the hippocampus was taken as the section in which the crura of the fornices departed from the lateral wall of the lateral ventricles (6, 18).

Intrarater variability for the measurements was 6.7% for the hippocampus and 7.4% for the entorhinal cortex (11, 19). The measurements were obtained without knowledge of the clinical data of the subjects. The volumes were normalized to the intracranial area measured at the level of the anterior commissure to exclude the effect of interindividual and intergender variability in the head size on the volumes studied (volume/intracranial area × 10^4) (6, 11).

Data Analysis

The data were analyzed by using SPSS for Windows (version 6.0). Student's *t*-test for independent samples was used to compare the differences in the volumes of the entorhinal cortices and hippocampi between control subjects and patients with Alzheimer disease. Discriminant function analysis (Wilks method) was performed to determine the accuracy of volume measurements in distinguishing Alzheimer patients from control subjects. The measured volumes were included independently in the statistical analysis to determine which of the variables best classified patients and control subjects; that is, maximizing the number of true positives and minimizing the number of false positives. In addition, gender was included in the final analysis, since gender has previously been reported to have an influence on the volumes (11).

The data were analyzed further by using ROC analysis (20), which evaluates the ability of methods to classify results and to compare the ability of different methods in detecting disease. Subjects can be classified into one of four groups according to the following ratings: true positive, when the test detects a true patient; false positive, when the test detects a control subject as a patient; true negative, when the test does not detect a control patient; and false negative, when the test does not detect a true patient. Thus, the sensitivity of the test is indicated by the number of all patients who have a positive test result as a percentage of all patients, and specificity is the number of control subjects who have a negative test result as a percentage of all control subjects. The ROC curve shows graphically the relationship between sensitivity and 1-specificity for each method. The ROC curve is further used to calculate the area under the curve (AUC) value, which is an index of overall discriminative ability of a given method. AUC values can be used to evaluate statistically different methods. In the present study, ROC analysis was used to determine which of the measured MR volumes would best distinguish patients with Alzheimer disease from healthy control subjects. First, the volumes of each measured region were divided into intervals of 10%, and then these intervals were used to determine the number of subjects whose volumes were below that interval and the number of subjects whose volumes were above it. Finally, AUC values from each curve were compared to find out which area would maximize the number of patients with true Alzheimer disease and minimize the number of control subjects with false-positive results.

To analyze the relative magnitude of difference in hippocampal and entorhinal volumes between patients and control subjects, we used MANOVA for repeated measures, in which we included standardized ([volume − control volume mean]/control volume SD) left hippocampal and left entorhinal volumes as a repeated measure (within subject factor), and the diagnostic category as a grouping factor.

Results

On both sides, a statistically significant difference between patients with Alzheimer disease and control subjects ($P < .001$) was determined in the mean volumes of both the entorhinal cortices and

Discriminant classification of patients with Alzheimer disease and control subjects

Measured MR Volumes	Sensitivity (%)	Specificity (%)	Overall Correct Classification (%)
Hippocampus	80	91	86
Entorhinal cortex	80	94	87
Hippocampus and gender	87	94	90
Entorhinal cortex and gender	90	94	92

the hippocampi. Compared with that in control subjects, the volume of the entorhinal cortex in patients with Alzheimer disease was 40% smaller on the left and 38% smaller on the right. The volume decrease in the hippocampus was 35% and 33%, respectively.

Discriminant function analyses were applied to the volumes of the hippocampus and entorhinal cortex to test their accuracy in distinguishing Alzheimer patients from healthy control subjects. The sensitivity and specificity values and the overall accuracy of volumes to distinguish Alzheimer patients from control subjects are presented in the Table 1. First, volumes of the right and left entorhinal cortex and the right and left hippocampus were included independently in the discriminant analysis. The volume of the right hippocampus yielded a sensitivity of 77% and a specificity of 84% (Wilks $\lambda = 0.52$; $\chi^2 = 38.63$; $df = 1$, $P < .0001$), whereas the volume of the left hippocampus yielded a sensitivity of 80% and a specificity of 90% (Wilks $\lambda = 0.41$; $\chi^2 = 53.12$; $df = 1$, $P < .0001$). Classification of the subjects by means of the volume of the right entorhinal cortex resulted in 80% sensitivity and 88% specificity (Wilks $\lambda = 0.52$; $\chi^2 = 38.63$; $df = 1$, $P < .0001$); classification by means of the volume of the left entorhinal cortex resulted in 80% sensitivity and 84% specificity (Wilks $\lambda = 0.54$; $\chi^2 = 36.81$; $df = 1$, $P < .0001$). Next, the volumes of the right and left hippocampus were included in one analysis and those of the right and left entorhinal cortex in another. Classification of the subjects by using the volume of the hippocampi resulted in a sensitivity of 80% for Alzheimer patients 91% for control subjects (Wilks $\lambda = 0.41$; $\chi^2 = 53.32$; $df = 2$, $P < .0001$). Classification by using the volume of the entorhinal cortices correctly identified 80% of the Alzheimer patients and 94% of the control subjects (Wilks $\lambda = 0.47$; $\chi^2 = 44.84$; $df = 2$, $P < .0001$). Finally, because gender has been found to have an effect on volume (11), sex was also included in the discriminant function analysis together with volume. Figure 1 displays the scatter plots and the mean and SD of the volumes of the right and left hippocampus and entorhinal cortex by groups and by sex. In the anal-

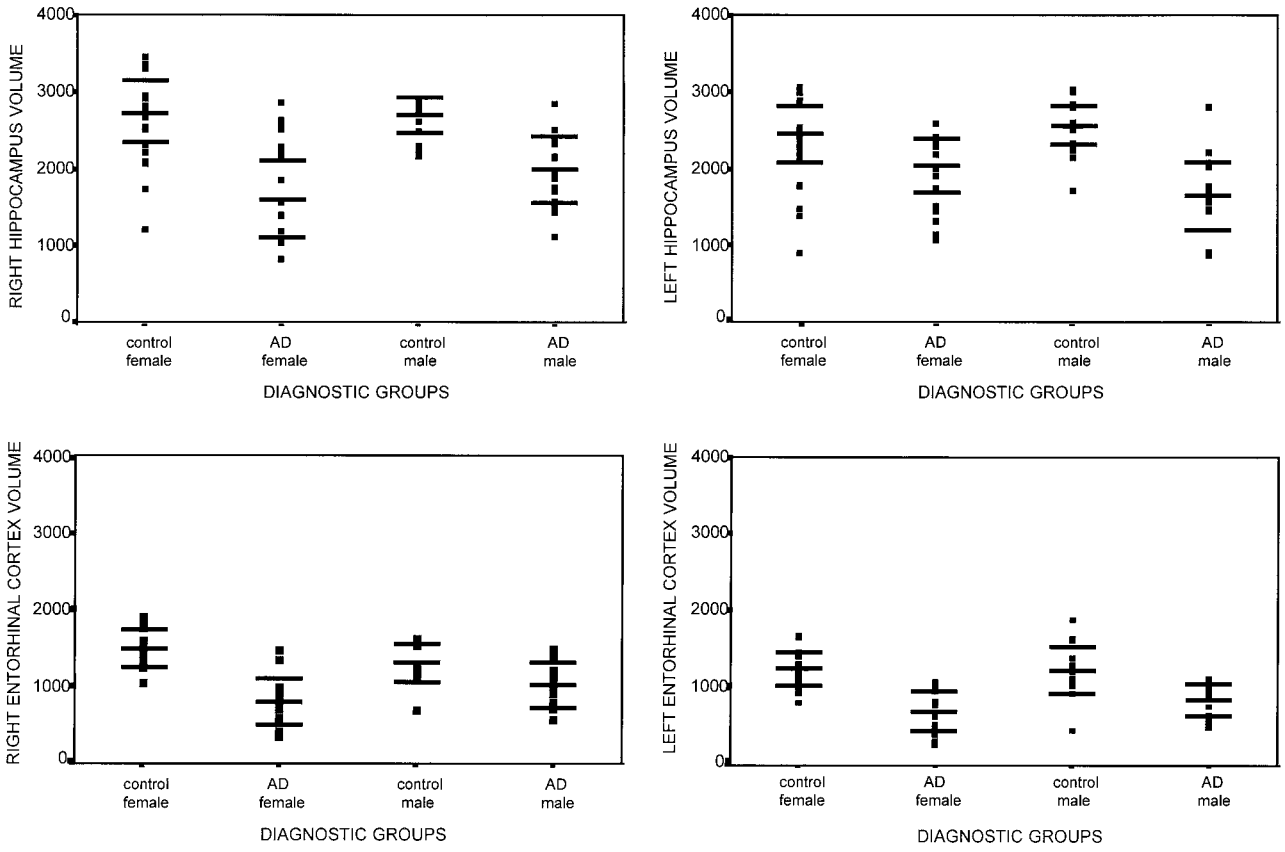

FIG 1. Scatter plots and mean ± SD of the volumes of the right and left hippocampus (*top*) and right and left entorhinal cortex (*bottom*) for both sexes in control subjects and patients with Alzheimer disease.

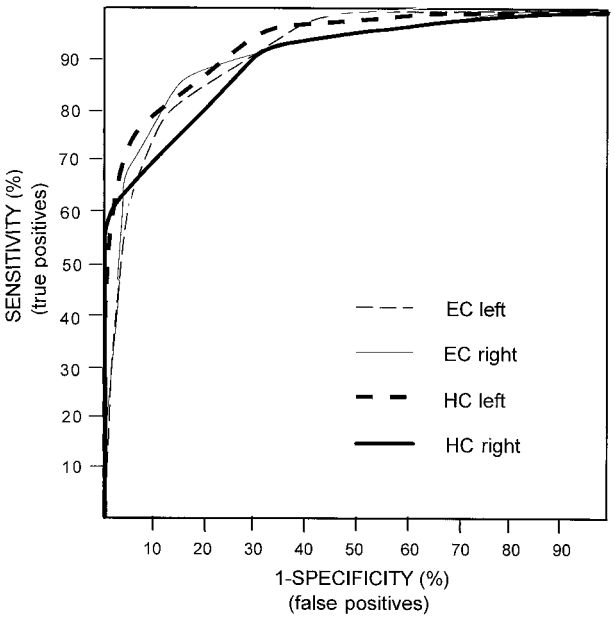

FIG 2. ROC curves of the left and right volumes of the entorhinal cortex and hippocampus in the diagnosis of Alzheimer disease.

ysis including gender and right and left hippocampi, 30 (94%) of 32 control subjects and 26 (87%) of 30 Alzheimer patients were correctly classified, yielding an overall correct classification of 90% (Wilks $\lambda = 0.38$; $\chi^2 = 55.85$; $df = 3$, $P < .0001$). The best classification was achieved by using the volumes of the entorhinal cortex and gender, resulting in the correct classification of 30 (94%) of 32 control subjects and 27 (90%) of 30 Alzheimer patients (Wilks $\lambda = 0.46$; $\chi^2 = 45.95$; $df = 3$, $P < .0001$), for an overall correct classification of 92%.

Figure 2 shows the ROC curves of the entorhinal cortices and the hippocampi. Since it shows the relationship between sensitivity and 1-specificity, the best combination of these values is represented with the curve nearest to the top left corner. The AUC value, representing the overall ability of the measured volume to discriminate patients from control subjects, was 0.94 for the left hippocampus and 0.91 for the right hippocampus. The AUC value for both the right and left entorhinal cortices was 0.91. None of these AUC values provided significantly better discriminatory values than the other values ($P > .05$).

The MANOVA for repeated measures on standardized left hippocampal and left entorhinal volume within subject factor and diagnostic category (Alzheimer patients/control subjects) as a grouping factor showed significant effect on group ($F = 7.59$, $P = .008$) and also a significant region × group interaction ($F = 7.64$, $P = .008$). The examination of the mean and SD of standardized values favored hippocampal volumetry (-0.0002 ± 1.0006 for control subjects and -2.532 ± 1.1426 for Alzheimer patients over entorhinal volumetry (-0.0016 ± 1.0013 for control subjects and -1.7206 ± 0.8778 for Alzheimer patients).

Discussion

Our results suggest that in addition to the hippocampal volumetry, the volumetric measurement of the entorhinal cortex is valuable in distinguishing patients with Alzheimer disease from control subjects. In the discriminant function analysis, volumetry of the entorhinal cortex yielded a specificity of 94% with a sensitivity of 90% in distinguishing Alzheimer patients from control subjects. Corresponding results were obtained with the volume of the hippocampus. No essential difference was found in the discriminative power of entorhinal and hippocampal volumetry. The best sensitivity was achieved by including gender with the volume of the entorhinal cortex; this also yielded the highest overall accuracy of 92% in distinguishing control subjects from Alzheimer patients.

We also used ROC analysis to compare the diagnostic value of volumetry of the entorhinal cortex and the hippocampus in detecting Alzheimer disease. The ROC curve shows the overall discriminative power indicated by the AUC. The volumes of both the hippocampus and the entorhinal cortex provided high AUC values, indicating considerably good overall discriminant ability. In this analysis, the left hippocampus had the largest AUC value, although the difference was not statistically significant compared with other measurements.

However, MANOVA for repeated measures, including standardized left hippocampal and left entorhinal volumes, within subject factor and diagnostic category as a grouping factor had significant effect on group and also a significant region × group interaction in favor of hippocampal volumetry. This finding suggests that hippocampal volumetry that yields less variability and is technically easier might be more feasible in Alzheimer disease diagnostics.

Our results agree with findings of previous investigators reporting the reliability of volumetric MR imaging of the hippocampus, and particularly with the added value of combined measurements of medial temporal lobe structures, in distinguishing Alzheimer patients from control subjects. For example, Kesslak et al (1) measured the volume of the hippocampus and the parahippocampal gyrus in eight patients with Alzheimer disease and seven control subjects and found no overlap between the groups. Similarly, a complete distinction of eight patients with Alzheimer disease from seven control subjects was obtained by using the volume of the hippocampus combined with the temporal horn of the lateral ventricle (4). In another study, Lehéricy et al (5) achieved 100% accuracy in identifying patients with Alzheimer disease ($n = 18$) and control subjects ($n = 8$) by using the combination of the volumes of the amygdala and the hippocampus, but the accuracy rate was lower for the hippocampus

alone. Pearlson et al (3) also reported that a combination of the volumes of the temporal lobe structures is more reliable than any single measure alone. In that study, the superiority of the volume of the entorhinal cortex and the amygdala (accuracy, 81%) over the hippocampal volume in diagnosing Alzheimer disease was reported in eight Alzheimer patients and nine control subjects, suggesting that volumes other than that of the hippocampus may be more accurate in distinguishing Alzheimer patients from healthy control subjects. Indeed, our data further extend these findings and establish that measurement of the volume of the entorhinal cortex also yields high discriminative power between Alzheimer patients and control subjects.

Although completely accurate discrimination between patients with Alzheimer disease and control subjects has been achieved in some of the volumetric studies, the sample sizes in those studies have been small. With a larger sample size, we found some overlap between Alzheimer patients and control subjects. On the one hand, the results of this study are comparable to those of previous studies of hippocampal volumes showing high but incomplete discrimination between Alzheimer patients and control subjects (2, 6, 7). On the other hand, the clinical diagnosis of Alzheimer disease is not accurate (21), particularly at the onset of symptoms, and the definite diagnosis of Alzheimer disease can only be confirmed by neuropathologic assessment. Furthermore, since pathologic studies have suggested that neuropathologic changes might appear years before clinical diagnosis of Alzheimer disease is possible, some overlap between the groups may be explained by incipient Alzheimer disease in some control subjects.

Apart from differentiating Alzheimer disease from normal aging, volumetry of the hippocampus seems to be useful in differentiating Alzheimer disease from other diagnostic conditions, such as age-associated memory impairment (6) and depressive pseudodementia (22). Data on entorhinal atrophy in other dementias are sparse.

Identification of subjects at high risk for Alzheimer disease is a challenge. Memory impairment is usually the first symptom of Alzheimer disease, but it is not easy to distinguish benign memory problems from those that are precursors of Alzheimer disease. In incipient Alzheimer disease, diagnostic support of volumetric MR imaging of the hippocampus and the entorhinal cortex may be of great value. Previous pathologic studies have suggested that neuropathologic hallmarks, such as neurofibrillary tangles, first accumulate in the entorhinal cortex and thereafter in the hippocampus (9, 10). Moreover, as the number of tangles may correlate highly with atrophy (23), volume loss would be expected to occur, especially in these regions at the earliest stages of disease. Indeed, our results support the pathologic data by establishing pronounced atrophy in vivo in the entorhinal cortex and the hippocampus in patients with Alzheimer disease.

Conclusion

The findings of this study establish that volumetric measurements of the entorhinal cortex and the hippocampus have a comparably high discriminative power to distinguish patients with mild to moderate Alzheimer disease from healthy elderly subjects. In our patient population, MANOVA for repeated measures favored hippocampal volumetry over entorhinal volumetry. Further longitudinal studies, however, are needed to determine whether volumetry of the entorhinal cortex is more sensitive than hippocampal volumetry in detecting incipient Alzheimer disease.

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