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Volumetric MRI Measurements Can Differentiate Alzheimer's Disease, Mild Cognitive Impairment, and Normal Aging

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ABSTRACT. *Background:* Volumetric magnetic resonance imaging (MRI) has been extensively studied in the last decade as a method to help with the clinical diagnosis of Alzheimer's disease (AD). In recent years, researchers have also started investigating if that technique would be useful to identify individuals with mild cognitive impairment (MCI), differentiating them from AD patients and from normal elderly controls. This research project was planned to assess the accuracy of volumetric MRI to differentiate those groups of individuals. *Method:* The investigation involved 39 patients with diagnosis of mild to moderate dementia in AD, according to the criteria of the NINCDS-ADRDA, DSM-III-R, and ICD-10; 21 subjects with complaints of cognitive decline without other psychiatric disorders (MCI); and 20 normal elderly controls. All the subjects were submitted to a standard protocol, including volumetric MRI evaluations. *Results:* The results indicated that all regions of interest measured (amygdala, hippocampus, and parahippocampal gyrus) were significantly different ($p \leq .005$) in AD patients compared to MCI subjects and controls. The left volumetric measures (amygdala, hippocampus, and parahippocampal gyrus) were also significantly different between the MCI subjects and controls ($p < .05$). The discriminant function analysis correctly classified 88.14% of the AD patients and controls, 81.67% of AD patients and MCI subjects, and 80.49% of the MCI subjects and controls. *Conclusions:* The results suggest that measures of medial temporal lobe regions are useful to identify mild to moderate AD patients and MCI subjects, separating them from normal elderly individuals.

KEYWORDS: Alzheimer's disease; mild cognitive impairment; aging; magnetic resonance imaging; diagnosis

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Many magnetic resonance imaging (MRI) studies published in the last years showed a consistent involvement of temporal lobe structures early in the course of Alzheimer's disease (AD). O'Brien (1995) reviewed 10 of such studies and summarized that temporal lobe MRI has a sensitivity and specificity of 85% to 95% to differentiate patients with even mild AD from controls. Some authors have investigated the utility of temporal lobe volumetric measures to differentiate subjects with mild cognitive impairment (MCI) from normal controls (Convit et al., 1993, 1995; Kaye et al., 1997; Parnetti et al., 1996; Soininen et al., 1994). Other studies have showed that hippocampal atrophy correlated with memory tests in MCI subjects (Soininen et al., 1994), elderly controls (Golomb et al., 1994), and AD patients (Deweer et al., 1995; Laakso et al., 1995b). In a review, it was possible to conclude that individuals at risk for AD as MCI subjects display structural and functional abnormalities especially in the temporal and parietal lobes (Bottino & Almeida, 1997). The correct identification of mild AD cases is very important for obtaining good therapeutic results. The investigation of "at risk" individuals can help find suitable candidates for drug trials, providing patients and families with more accurate information on the prognosis and management of the disease.

In this study, AD patients, MCI subjects, and normal elderly controls were compared using volumetric MRI measures of temporal lobe structures in order to investigate the accuracy of this technique in classifying those groups of individuals. The correlation between the volumetric data with results of the cognitive tests applied to the subjects was also investigated.

METHODS

Subjects

A group of 39 AD patients (34 probable AD and 5 possible AD) was examined, diagnosed according to NINCDS-ADRDA (McKhann et al., 1984) and ICD-10 (World Health Organization, 1992) criteria, with Mini-Mental State Examination (MMSE) score $\geq$ 14 (Folstein et al., 1975). The patients were classified as mild (n = 31; 79.5%) or moderate AD (n = 8; 20.5%), according to DSM-III-R (American Psychiatric Association, 1987). Another 21 individuals classified as MCI according to modified ICD-10 criteria (e.g., complaints of cognitive function decline *for at least 6 months*, without any other psychiatric diagnosis or significant functional impairment) with MMSE score $\geq$ 24 were also examined. The AD and MCI individuals were outpatients from the Old Age Research Group ambulatory at the Institute of Psychiatry in São Paulo, consecutively admitted from 1994 to 1996. Twenty normal elderly controls (without cognitive complaints or psychiatric disorders) were evaluated, with MMSE score $\geq$ 28. Patients with controlled systemic disorders such as hypertension, diabetes, or hypercholesterol were also accepted for the control group. All the controls were outpatients from the Geriatric Service of the "Hospital das Clínicas da FMUSP," in São Paulo, evaluated from 1995 to 1996.

The exclusion criteria were history or clinical/radiological evidence of stroke; other neurological diseases (e.g., Parkinson's disease); and severe medical diseases (e.g., cancer; hepatic, metabolic, or renal disorders). All the subjects studied were at least 55 years old.

Table 1 shows the demographic characteristics of the 80 subjects examined, which were matched for gender. AD patients were older than the other two groups, but the initial difference on analysis of variance (ANOVA) did not persist after correction for multiple comparisons. Other demographic characteristics (years of education, marital status, and social class) were not significantly different between the groups.

All subjects were submitted to the following protocol: psychiatric and medical history; work-up for the differential diagnosis of dementia (complete blood count with differential; renal, liver, and thyroid function tests; vitamin B_{12} and folic acid levels; test for syphilis; urinalysis); physical and neurological examination; application of the CAMDEX, CAMCOG (Roth et al., 1986), and the Handedness inventory (Annett, 1967); cranial computerized tomography (only for AD patients); clinical diagnosis according to the criteria mentioned; volumetric MRI. All subjects (and/or their legal caregivers) gave informed written consent to participate in this project, which was approved by the Ethics Committee of the School of Medicine of the University of São Paulo.

Cognitive Assessment

The results of the MMSE, the CAMCOG, and the CAMCOG memory subscale applied to the three groups of subjects were compared. According to the Handedness inventory, the subjects were classified as right-handed (AD: 37; MCI: 20; Controls: 18) or non-right-handed (AD: 2; MCI: 1; Controls: 2). Table 2 shows the cognitive tests' results.

MRI Methodology

Volumetric MRI examinations were performed on a 1.5-tesla Phillips Gyroscan Scanner (Phillips International, Einhoven, Holland) and recorded on magneto-optical disks for posterior analysis. The slices were acquired according to the following protocol: (a) 18 T1 axial slices (repetition time [TR]: 655; echo time [TE]: 13; field of view [FOV]: 230), 0.6 cm thick with 0.06 cm gap, and 18 T2 axial slices (TR: 2,500; TE: 25; FOV: 230), 0.6 cm thick with 0.06 cm gap, for the clinical diagnosis; (b) 15 T1 sagittal slices (TR: 500; TE: 14; FOV: 240), 0.6 cm thick with 0.06 cm gap; (c) 64

TABLE 1. Demographic Data

	AD (n = 39)	MCI (n = 21)	Controls (n = 20)	Statistical Test
Age				
Mean (*SD*)	73.08 (7.21)	69.52 (5.58)	69.15 (4.84)	F = 3.54
95% CI	70.74–75.41	66.98–72.06	66.89–71.41	p = .034*
Sex, n (%)				
Female	25 (64.1)	15 (71.4)	14 (70)	χ^2 = 0.41
Male	14 (35.9)	6 (28.6)	6 (30)	p = .81
Education, years				
Mean (*SD*)	5.69 (4.19)	7.62 (4.33)	6.45 (3.56)	F = 1.52
95% CI	4.33–7.05	5.65–9.59	4.78–8.12	p = .224

Note. AD = Alzheimer's disease; CI = confidence interval; MCI = mild cognitive impairment.
*AD versus controls, p = .066.

TABLE 2. Cognitive Tests' Results

Tests	AD (n = 39)	MCI (n = 21)	Controls (n = 20)	ANOVA
MMSE				F = 82.39
Mean	20.21*, **	26.48***	29.15	p < .001
SD	3.61	1.78	0.75	
95% CI	19.03–21.38	25.67–27.29	28.8–29.5	
CAMCOG				F = 67.72
Mean	60.45*, **	82.24****	91.45	p < .001
SD	12.68	9.32	4.86	
95% CI	56.28–64.61	78–88.48	89.17–93.73	
CAMCOG memory subscale				F = 88.25
Mean	10.33*, **	19.38****	22.10	p < .001
SD	4.29	3.02	2.17	
95% CI	8.94–11.72	18.00–20.76	21.08–23.12	

Note. AD = Alzheimer's disease; ANOVA = analysis of variance; CAMCOG = Cambridge Cognitive Examination; CI = confidence interval; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination.
*AD versus MCI: p < .001. **AD versus controls: p < .001. ***MCI versus controls: p < .01. ****MCI versus controls: p < .05.

T1 coronal slices (TR: 30; TE: 9; FOV: 240), 1.2 mm thick, no gap, volume by the "fast-field echo" (FFE) technique, perpendicular to the hippocampal axis.

The images were transferred to a Phillips Workstation and the regions of interest (ROI: amygdala, hippocampus, and parahippocampal gyrus) were drawn bilaterally on enlarged coronal slices using proprietary software (Gyroview). All the image analyses were done blind to patient name and group membership. The structures were outlined with a mouse-driven cursor and the areas obtained in each slice were summed up and multiplied for the slice thickness to estimate the raw volume (RV). A measure of the intracranial area (IC) obtained from a sagittal slice was used as an index of the head size (Cuénod et al., 1993). All raw volumes were corrected for head size interindividual differences to estimate the corrected volumes (CV) with the formula:

$$CV = \frac{RV}{IC} \times 100$$

The anatomical landmarks used by the observers to identify each structure were defined upon the Duvernoy (1988) atlas and published studies on the same topic (Deweer et al., 1995; Jack et al., 1992; Pearlson et al., 1992; Watson et al., 1992).

The ROI measured from anterior to posterior coronal slices were outlined as follows:

Amygdala. Amygdala was defined as the grey-matter region seen in the medial superior portion of the temporal lobe. The anterior part of each amygdala (right and left) was measured from the slice where the collateral sulcus closes to constitute the endorhinal sulcus. The entorhinal cortex inferior to the uncal notch was excluded from the measures of the amygdala. When the uncal notch was not visible, the separation of the amygdala from the entorhinal cortex was done by drawing a line from the amygdala inferior border. The inferior and lateral boundaries were

defined as the inferior horn of the lateral ventricle or the temporal lobe white matter. The superior part was defined by drawing a straight line laterally to the endorhinal sulcus up to the inferior part of the insula. On posterior slices, the superior boundary was outlined by drawing a straight line from the superior-lateral part of the optical tract to the inferior part of the insula. The amygdalas were drawn bilaterally up to the slice showing a grey-matter region on the medial portion of the hoof of the lateral ventricle inferior horn. The amygdala was measured in all consecutive slices where it could be identified according to the description above. The median number of slices measured for the amygdala (on both sides) was 12.

Hippocampus. This complex structure projects itself inside the temporal horn of the lateral ventricle and can be divided in three parts: head, body, and tail. The hippocampus was outlined bilaterally from the first slice where it was possible to see a small portion of grey matter below the amygdala and above the parahippocampal gyrus. The most reliable landmark to separate the hippocampus from the amygdala in that region was the inferior horn of the lateral ventricle, especially when the uncal recess was visible. However, when the uncal recess was not visible, hippocampus and amygdala were separated according to one of the following rules: drawing a line connecting the inferior horn of the lateral ventricle to the inferior boundary of the semianular gyrus; using the alveus to separate the hippocampus from the amygdala; or, when neither of these structures was present, drawing a horizontal line connecting the plane of the inferior horn of the lateral ventricle to the uncus surface. The inferior part of the hippocampus was outlined including the subiculum and the uncal notch, being the inferior boundary defined by the white matter of the parahippocampal gyrus. The body of the hippocampus was measured including the subiculum, Ammon's horn, dentate gyrus, and the fimbria. The last slice measured was the one immediately before the crux of the fornix, visible in all its extension. The hippocampus was measured in every consecutive slice where it could be identified according to the description above. The median number of slices measured for the hippocampus (on both sides) was 16.

Parahippocampal Gyrus. This structure was defined as the band of grey and white matter situated in the medial-inferior temporal lobe, having as superior boundary, the uncus; as inferior boundary, the rhinal sulcus; and as lateral boundary, the white matter of the temporal lobe. The parahippocampal gyrus was outlined bilaterally from the first slice where the hippocampus was drawn. The superior limit was the line already drawn to outline the hippocampus, following the white matter of the parahippocampal gyrus. The inferior boundary was defined as the rhinal sulcus. The lateral boundary was defined by tracing a straight line from the most profound part of the parahippocampal gyrus's grey matter up to the superior boundary where the hippocampal drawing started. The parahippocampal gyrus was outlined up to the last slice immediately before the cingulate gyrus was visible in all its extension in each hemisphere. The parahippocampal gyrus was measured in every consecutive slice where it could be identified according to the

description above. The median number of slices measured for the parahippocampal gyrus (on both sides) was 13.

Intracranial Area. The intracranial cross-sectional area was measured in one middle sagittal slice delimited by a line drawn along the internal table of the skull. Two examiners (C. M. C. B. and R. L. M.) measured independently the ROI of 10 subjects and one examiner (R. L. M.) measured twice the same subjects to evaluate the reliability of the anatomical landmarks used. The intraclass correlation coefficient (ICC) results indicated a good interobserver agreement on all ROI measured (amygdala: .79; hippocampus: .86; parahippocampal gyrus: .76; $p < .001$) and an excellent intrarater agreement for the amygdala and hippocampus (amygdala: .94; hippocampus: .98; $p < .001$).

Statistical Analysis

Statistical analysis was done with the Statistical Package for the Social Sciences, version 6.0 for Windows (SPSS Inc., 1993). The frequencies of categories (gender) were compared using the chi-square and the Mantel-Haenszel tests. The continuous data (age, education, cognitive tests, and volumetric measures) were compared with ANOVA and Tukey's test for post hoc analysis. The volumetric measures corrected for age were compared through the analysis of covariance (ANCOVA). A discriminant function analysis in which all structures were entered as independent factors was done in order to investigate which ROI or combination of ROIs would best discriminate the three groups of individuals. The Pearson correlation coefficient was used to investigate the correlation between the results of the cognitive tests and the volumetric measures.

RESULTS

The results obtained with the mean intracranial area of each group and the adjusted volumetric measures are presented in Table 3. The mean intracranial area did not differ significantly between the groups. On the other hand, all the medial temporal lobe structures on both sides were significantly different between AD patients and controls ($p < .001$). The structures measured on the left side (left amygdala; left hippocampus; left parahippocampus) were also significantly different between MCI subjects and controls ($p < .05$). Another analysis was run with age as a covariate (ANCOVA), and the differences remained the same after correction for age.

A discriminant function analysis was done to investigate which combination of structures would show the highest percentage of sensitivity, specificity, and correct classification, of the three groups examined. These results are presented in Table 4.

Table 5 shows the correlation observed between the results of cognitive tests and the results of the volumetric measures. Many significant correlations were found ($p \leq .001$), particularly between the MMSE, CAMCOG–total, some CAMCOG subscales (orientation and memory), and the volumetric measures.

CONCLUSIONS

Some limitations of this research should be mentioned. The volumetric measures did not include other cerebral structures and therefore the observed differences can uniquely represent generalized brain atrophy, not medial temporal lobe atrophy. Another possible

source of error when interpreting the results would be the only "good" inter-rater reliability observed. However, the intrarater reliability for the amygdala and the hippocampus was excellent, and even higher than that reported in similar studies (Killiany et al., 1993; Pearlson et al., 1992).

Table 3 shows that the mean of all ROI measured (on both sides) in our study was significantly different between AD patients and MCI subjects. Besides that, the mean volume of the structures on the left side was also significantly smaller for the MCI group compared to the control group. In Table 6, nine studies that compared AD, MCI, and control subjects are summarized.

The first difficulty in comparing the results of these studies is the difference between terms and diagnostic criteria employed by the authors to identify the

TABLE 3. Results of the Adjusted Volumetric Measures

ROI	AD (n = 39)	MCI (n = 21)	Controls (n = 20)	ANOVA
Right amygdala				
Mean	9.78*, **	12.51	14	F = 26.34
SD	2.23	2.52	1.88	p < .001
95% CI	9.06–10.5	11.36–13.66	13.12–14.88	
Left amygdala				
Mean	9.07****, **	11.62***	13.74	F = 23.61
SD	2.49	2.54	2.6	p < .001
95% CI	8.27–9.88	10.47–12.78	12.53–14.96	
Right hippocampus				
Mean	21.72*, **	25.16	27.27	F = 21.99
SD	3.54	1.67	3.61	p < .001
95% CI	20.57–22.86	24.4–25.92	25.58–28.96	
Left hippocampus				
Mean	20.88****, **	24.2***	27.05	F = 25.7
SD	3.49	2.93	2.84	p < .001
95% CI	19.75–22.01	22.86–25.53	25.72–28.38	
Right parahippocampal gyrus				
Mean	12.65****, **	15.11	16.51	F = 18.16
SD	2.59	1.99	2.57	p < .001
95% CI	11.81–13.49	14.21–16.02	15.31–17.71	
Left parahippocampal gyrus				
Mean	12.88*****, **	15.28***	17.84	F = 22.15
SD	2.74	2.29	3.15	p < .001
95% CI	11.99–13.77	14.24–16.32	16.37–19.32	
Intracranial area				
Mean	14,891.4	14,952.1	14,568.7	F = 0.52
SD	1,519.81	1,147.39	1,037.32	p = .6
95% CI	14,398.7–15,384.1	14,429.8–15,474.4	14,083.2–15,054.2	

Note. ROI = regions of interest; other abbreviations as in Table 2.
*AD versus MCI: p < .001. **AD versus controls: p < .001. ***MCI versus controls: p < .05. ****AD versus MCI: p = .001. *****AD versus MCI: p = .005.

TABLE 4. Discriminant Function Analysis With the Volumetric Measures

Groups	*n*	ROI	SENS	SPEC	Accuracy
AD vs. controls	59	RAM, LH	89.7%	85%	88.14%
AD vs. MCI	60	RAM, RH	87.2%	71.4%	81.67%
Mild AD vs. MCI	52	RH, LAM	80.6%	71.4%	76.92%
MCI vs. controls	41	LH	81%	80%	80.49%

Note. SENS = sensitivity; SPEC = specificity; RAM = right amygdala; LH = left hippocampus; RH = right hippocampus; LAM = left amygdala; other abbreviations as in Table 2.

TABLE 5. Correlation Between Cognitive Tests and Volumetric Measures

	Volumetric Measures Pearson Correlation Coefficients					
Cognitive Tests	RAM	LAM	RH	LH	RPH	LPH
MMSE	.58*	.50*	.54*	.56*	.53*	.56*
CAMCOG	.54*	.50*	.47*	.50*	.47*	.50*
Orientation	.51*	.43*	.50*	.52*	.49*	.52*
Language	.40*	.36*	.29***	.30***	.31***	.32**
Memory	.61*	.56*	.64*	.65*	.60*	.59*
Attention	.38*	.40*	.33**	.35**	.29***	.40*
Praxis	.33**	.34**	.19	.22****	.21	.28****
Calculation	.34**	.26****	.32**	.32**	.31**	.37*
Abstract thinking	.21	.20	.12	.17	.13	.16
Perception	.20	.13	.07	.10	.13	.17

Note. LPH = left parahippocampal gyrus; RPH = right parahippocampal gyrus; other abbreviations as in Table 2.
*$p \leq .001$. **$p \leq .005$. ***$p \leq .01$. ****$p \leq .05$.

minimally impaired individuals. In four studies (Laakso et al., 1995b, 1998; Parnetti et al., 1996; Soininen et al., 1994), the patients were selected according to age-associated memory impairment (AAMI) criteria (Crook et al., 1986), whereas Convit and colleagues (1993, 1995, 1997) classified them as mildly cognitive impaired, Kaye and coworkers (1997) classified them as subjects with preclinical dementia, and Visser and colleagues (1999) used the term "minimal dementia" from the CAMDEX interview (Roth et al., 1986).

The authors used volumetric MRI to investigate MCI subjects, but the techniques for image acquisition and processing were quite different, and so were the anatomical parameters to identify the ROI. The slices acquired were quite thick (4 mm or more) in six out of nine reports reviewed, and this detail could have influenced the results obtained. Two groups of researchers were responsible for six of these nine studies. Convit and colleagues (1993, 1995, 1997) from the New York University (NYU) reported significant differences between MCI

TABLE 6. Summary of Nine Volumetric MRI Studies in Mildly Cognitively Impaired Individuals

Authors	Subjects (Mean Age)	Results: AD vs. MCI	Results: MCI vs. Controls
Convit et al. (1993)	15 AD (70.8) 17 MCI (73.8) 18 controls (68.4)	H; PHG; FG; MITG & STG: *ns*	H: $p < .05$
Soininen et al. (1994)	16 AAMI (67.7) 16 controls (70.2)		AM (R,L) & H (R,L): *ns* H (R minus L): $p < .05$
Convit et al. (1995)	22 MCI (74.2) 27 controls (69.3)		H: $p < .01$; PHG; FG; MITG & STG: *ns*
Laakso et al. (1995b)	54 AD (70) 38 AAMI (70) 34 controls (72)	AM (R/L): $p < .05$	AM (R/L): *ns*
Parnetti et al. (1996)	6 AD 6 AAMI 6 controls	H (R+L): *ns*	H (R+L): $p < .02$
Kaye et al. (1997)	12 PreD (86.8) 18 controls (90.4)		R H; $p < .0014$; L H: $p < .048$; H (R+L): $p < .0018$
Convit et al. (1997)	27 AD (72.3) 22 MCI (74.1) 27 controls (69.3)	PHG; FG: SD H; MITG; STG & BA: *ns*	H: SD PHG; FG; MITG; STG & BA: *ns*
Laakso et al. (1998)	55 AD (70) 44 AAMI (70) 42 old controls (72)	R H; L H; R H/coronal ICA; L H/ coronal ICA; R H/sagittal ICA; L H/sagittal ICA: $p < .0001$ R H area; L H area: *ns*	R H; L H; R H/coronal ICA; L H/coronal ICA; R H/sagittal ICA; L H/sagittal ICA; R H area; L H area: *ns*
Visser et al. (1999)	7 AD (79.6) 20 MD (78.8) 18 controls (76.8)	H (R+L); PHG (R+L); LTL (R+L); ICA: *ns*	H (R+L); PHG (R+L); LTL (R+L); ICA: *ns*

Note. AD = Alzheimer's disease; MCI = mild cognitive impaired; H = hippocampus; PHG = parahippocampal gyrus; FG = fusiform gyrus; MITG = medial-inferior temporal gyrus; STG = superior temporal gyrus; *ns* = not significant; AAMI = age-associated memory impaired; AM = amygdala; R = right; L = left; PreD = preclinical dementia; SD = significantly different; BA = brain atrophy; ICA = intracranial area; MD = minimal dementia; LTL = lateral temporal lobe; MRI = magnetic resonance imaging.

individuals and controls, especially regarding the hippocampus. On the other hand, the group from the University of Kuopio in Finland (Laakso et al., 1995b, 1998; Soininen et al., 1994) stated that the temporal lobe measures could help separate AD patients from AAMI subjects, but not AAMI individuals from controls. Analyzing them, a hypothesis was raised that many elderly subjects complaining of normal cognitive decline formed the AAMI group studied in Finland, whereas the researchers from NYU managed to select a group with a "true" increased risk to develop dementia. The longitudinal results stated by Convit and colleagues (1997) in their publication lent support to this hypothesis: 7 out of 16 MCI subjects followed up with a mean interval of 2.4 years became demented, whereas all the controls remained nondemented in this period. On the other hand, the group from the University of Kuopio published a clinical follow-up (mean of 3.6 years) of 229 AAMI subjects, concluding that "in general, AAMI is nonprogressive, but the AAMI population also includes subjects with early dementia and subjects without genuine memory loss" (Hanninen et al., 1995). In regard to the other studies reviewed, Parnetti and colleagues (1996) reported significant differences between the hippocampus of AAMI subjects and controls, whereas Visser and coworkers (1999) did not find significant differences between their minimally demented (MD) group and the controls. Despite that, Visser and coworkers (1999) observed that the atrophy value of medial temporal structures in the MD group was situated between the values of the AD patients and the controls, as Parnetti and colleagues (1996) also pointed out in their study. Kaye and colleagues (1997) described the follow-up of 30 very old subjects evaluated annually during a mean period of 42 months, finding significant differences in the hippocampus (right and left) and significant time-dependent temporal lobe atrophy of the 12 subjects classified as predemented, compared to the 18 nondemented individuals.

Recently, Jack and coworkers (1999) reported interesting findings, investigating 80 MCI subjects of whom 27 became demented over a mean follow-up of 32.6 months. Hippocampal atrophy at baseline was associated with crossover from MCI to AD, with a relative risk (RR = .69, p = .015) that remained significant even when other variables (age, estrogen replacement, neuropsychological tests, APOE genotype, history of ischemic heart disease, and hypertension) were entered into bivariate analysis (Jack et al., 1999).

In the present study, all structures (hippocampus, amygdala, and parahippocampal gyrus) on both sides were significantly different between AD patients and MCI subjects, and all the structures on the left were also significantly smaller in the MCI group compared to the control group. The parahippocampal gyrus and the hippocampus on the left were the ROI that best discriminated the MCI group from the controls. Since the influential study of Braak and Braak (1991), the transentorhinal region was considered to be pathologically associated in cases of preclinical AD. In the present investigation, this region corresponded to a part of what was considered the parahippocampal gyrus. Braak and Braak (1991) suggested that in a later stage the pathological alterations would reach the entorhinal cortex and the hippocampus (the limbic stage), corresponding in clinical practice to

patients with incipient AD. The present study did not make it possible to consistently explain why the regions on the left were the best ones to discriminate the MCI group from the controls. These findings could solely be a result of selection bias. The number of left-handed patients in the sample was quite low (AD: 5.13%; MCI: 4.76%; Controls: 10%), especially in the AD and MCI groups, but such a finding could also be a result of selection bias. However, other authors have reported that left-handed individuals were underrepresented in late-onset AD compared to controls (Seltzer et al., 1984), or that a low risk for AD was associated with left-handedness in 74 twin pairs discordant for AD (Räihä et al., 1998). These findings give some support to the idea of a selective vulnerability of the left hemisphere in AD subjects. It is possible to hypothesize that in MCI subjects the atrophy would begin in the medial temporal lobe regions on the left, before spreading to the right hemisphere and to other regions in the brain (at least for those subjects in the sample who will develop dementia or AD in the future). Finally, further studies are necessary, of course, to confirm if a right hemisphere dominance might provide some protection against AD, as Räihä and colleagues (1998) have cautiously pointed out, and so are further studies showing laterality effects on cerebral regions of at-risk subjects for AD, to support the notion of a left hemisphere vulnerability suggested by the results of the present study.

Table 3 shows that the mean of all ROIs was significantly smaller in AD patients compared to elderly controls. Since the initial report of Seab and colleagues (1988), many authors have investigated the utility of the MRI volumetric measures to identify AD patients, separating them from controls (Cuénod et al., 1993; Ikeda et al., 1994; Jack et al., 1992, 1997; Juottonen et al., 1998; Kesslak et al., 1991; Killiany et al., 1993; Krasuski et al., 1998; Laakso et al., 1995a; Lehéricy et al., 1994; Pantel et al., 1997; Pearlson et al., 1992). All the studies reviewed used the NINCDS-ADRDA diagnostic criteria (McKhann et al., 1984) and applied some method of correction for head size differences between subjects. Another common characteristic was the magnetic field of the scanner: 1.5 tesla in all studies, except in the initial report of Seab and colleagues (1988). Despite the use of MRI volumetric methods, the techniques for image acquisition and processing were quite different, as well as the anatomical parameters for identifying the ROI.

The complete separation of AD patients from controls was achieved only in four studies, whereas some degree of overlapping was described in the remaining nine reports. All authors evaluated a certain temporal lobe region and particularly the measure of the hippocampus was made in 12 of the 13 reports, with the exception of Juottonen and coworkers' (1998) report. The results, considering the hippocampus, were quite consistent: only in Cuénod and colleagues' publication (1993) was the atrophy of the hippocampus not significantly different between AD patients and controls. Furthermore, the hippocampus was chosen as one of the ROI that best discriminated these two groups in 10 studies. The amygdala was the second most employed structure to separate both groups (it was cited in 7 of the 13 reports), and the combination of amygdala and hippocampus was described in 5 of the 13 studies reviewed.

Therefore, despite all the described differences, the articles reviewed and the results of the present research suggest that MRI volumetric measures of medial temporal lobe structures such as the hippocampus and the amygdala, and specifically a combination of both, are useful to help in the diagnosis of patients with mild to moderate AD, separating them from normal elderly controls with an accuracy range of 76% to 100%.

Table 5 shows the high correlation found in our sample between the medial temporal lobe structures and the results of tests applied to the patients, especially between the hippocampus volume on both sides (right hippocampus—r = .64; left hippocampus—r = .65; $p \leq .001$), and the CAMCOG memory subscale scores. Those results corroborated results of other studies that found correlation between hippocampal atrophy and memory tests in MCI subjects (Soininen et al., 1994), elderly controls (Golomb et al., 1994), and AD patients (Deweer et al., 1995; Laakso et al., 1995b). Golomb and colleagues (1994) reported that this significant correlation was found independent of age, gender, and generalized brain atrophy, stressing the role of the hippocampus as a structure contributing to the memory loss experienced by many aging individuals.

In conclusion, the results of this study indicate that volumetric MRI of medial temporal lobe regions is useful to identify mild to moderate AD patients and MCI subjects, separating them from normal elderly individuals. The results indicate that medial temporal lobe volumes of MCI individuals stand between those of AD patients and elderly controls, suggesting that these subjects are at risk for AD.

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