Hippocampus and Entorhinal Cortex in Frontotemporal Dementia and Alzheimer's Disease: A Morphometric MRI Study

Mikko P. Laakso, Giovanni B. Frisoni, Mervi Könönen, Mia Mikkonen, Alberto Beltramello, Claudia Geroldi, Angelo Bianchetti, Marco Trabucchi, Hilkka Soininen, and Hannu J. Aronen

Background: *Magnetic resonance imaging (MRI) of hippocampal atrophy is a sensitive but not specific method to support the clinical diagnosis of early Alzheimer's disease (AD). We recently described our findings that atrophy of the entorhinal cortex (ERC) in frontotemporal dementia (FTD) is equal to that found in AD but that hippocampal atrophy in FTD is less than that found in AD. The MRI volumes of these structures provide a topographic representation of the region of interest. We hypothesized that two different dementias with distinct histopathologic and clinical features might, in addition to quantitative patterns, display topographically different patterns of atrophy.*

Methods: *We adopted a morphometric approach to monitor the pattern of atrophy of the hippocampus and the ERC by computing two-dimensional profiles from MRI volumes of the structures in control subjects and patients with FTD and AD.*

Results: *Compared with control subjects, atrophy of the hippocampus in patients with AD was diffuse. In patients with FTD, atrophy of the hippocampus was localized predominantly in the anterior hippocampus, suggesting a different pattern of hippocampal atrophy in FTD compared with AD. The amount and pattern of atrophy of the entorhinal cortex was virtually equal in both demented groups.*

Conclusions: *This study provides novel data on the nature of medial temporal lobe atrophy in FTD. Morphometric MRI may be a useful technique for characterizing different patterns of atrophy in primary degenerative dementias in vivo.* Biol Psychiatry 2000;47:1056–1063 © *2000 Society of Biological Psychiatry*

Key Words: Alzheimer's disease, brain, dementia, entorhinal cortex, frontal lobe, magnetic resonance imaging, memory

Introduction

Alzheimer's disease (AD) has distinctive regional predilection and hierarchical topographic distribution of histopathologic changes within the medial temporal lobe (MTL) or, specifically, in the entorhinal cortex (ERC) and the hippocampus (Braak and Braak 1991; Gómez-Isla et al 1996; Hyman et al 1984). Although pathology of the MTL in AD is well documented, data on hippocampal atrophy on frontotemporal dementia (FTD) is much less consistent. FTD constitutes a heterogenic disorder, if not a spectrum of disorders, affecting mainly frontal and anterior temporal cortices and often lacking distinctive histopathologic markers found in other types of dementia (Brun 1987, 1993). With regard to the MTL, histopathologic studies on the hippocampus in FTD have shown the involvement of the hippocampus to range from severe (Knopman et al 1990) through modest or varying (Bergmann et al 1992; Nagaoka et al 1995) to minor or no involvement (Brun 1993; Filley et al 1994; Kinoshita et al 1997). Fewer data are available about the ERC.

The pathology of AD in the MTL leads to atrophy of the MTL structures, and volumetric magnetic resonance imaging (MRI) of hippocampal atrophy is a well-established tool to support the clinical diagnosis of early AD (Jack et al 1997; Laakso et al 1998). The atrophy may lack AD specificity, however. We recently have shown that in FTD, ERC atrophy is equal to that found in AD, but hippocampal atrophy is less in FTD than it is in AD (Frisoni et al 1999). The purpose of our article is to study whether different regions of interest (ROIs) with quantitatively different volume loss would also display topographically distinct patterns of volume loss. Indeed, there is an increased interest in morphometric brain mapping to study

From the Departments of Neurology (MPL, HS) and Clinical Radiology (MPL, MK, HJA), Kuopio University Hospital and the Department of Neuroscience and Neurology, University of Kuopio (MM, HS), Kuopio, Finland; IRCCS San Giovanni di Dio—FBF, Brescia, Italy (GBF, CG, ABi, MT); Institute of Radiology, University of Verona, Ospedale Borgo Roma, Verona, Italy (ABe); and the Department of Radiology, Helsinki University Central Hospital, Helsinki, Finland (HJA).

Address reprint requests to Mikko Laakso, Kuopio University Hospital, Department of Neurology, Bldg. 5, POB 1777, 70211 Kuopio, Finland.

Received August 3, 1999; revised November 30, 1999; accepted December 2, 1999.

0006-3223/00/$20.00
PII S0006-3223(99)00306-6

Table 1. Sociodemographic and Clinical Features of the Study Groups

	Frontotemporal dementia (n = 13)		Alzheimer's disease (n = 30)		Controls (n = 30)		
	$M \pm SD$ or n (%)	Range	$M \pm SD$ or n (%)	Range	$M \pm SD$ or n (%)	Range	p
Age (years)	62 ± 5^a	54–71	73 ± 9^b	53–86	69 ± 9^c	53–86	.0009
Gender (women)	3 (23%)^a		23 (77%)^b		20 (67%)^b		.003
Education (years)	7 ± 4^a	3–17	7 ± 4^a	2–18	8 ± 3^a	5–19	ns
ApoE ϵ4 allele^a	3/22 (14%)		19/56 (34%)		8/56 (14%)		ns
Age at disease onset	60 ± 5^a	52–69	70 ± 9^b	48–83	—		.0005
Disease duration (months)	30 ± 13^a	12–60	41 ± 25^a	9–80	—		ns
Mini-Mental State Examination	15 ± 8^a	0–29	20 ± 4^b	12–27	29 ± 1^c	25–30	<.0001
Clinical Dementia Rating scale							
0.5	6 (46%)		8 (27%)				ns
1	3 (23%)		14 (46%)				
2 to 3	4 (31%)		8 (27%)				
Disability							
Basic functions lost	0.8 ± 1^a	0–3	0.6 ± 1^a	0–4	0^b	0	.003
Instrumental functions lost	2.5 ± 2.4^a	0–8	3.7 ± 2.5^b	0–8	0^c	0	.003

p denotes significance of one-way analysis of variance or 3×2 χ^2 test. Figures with the same letter are not significantly different on Duncan's post hoc or 2×2 χ^2 test.

[a]Genotyping was not available for some subjects.

the topographic changes in relation to function and disease of the brain. For instance, researchers have suggested that three-dimensional mapping of the gyral patterns in the normal brain (Kennedy et al 1998) or in AD (Mega et al 1998) provide evidence of multiple influences of brain organization or cognition during development and disease. Topographic imaging may provide information about individual brain structures as an integral part of hierarchically ordered components of distributed neural systems. In addition, the hippocampus can be analyzed in terms of its topography. In a recent study, topographic mapping of the hippocampus revealed what appear to be specific regional volume deficits within the hippocampus in patients with schizophrenia (Csernansky et al 1998). No such data exists on the MTL structures in dementia.

In this study, we adopted a morphometric approach to assess the atrophy of the hippocampus and the ERC in FTD, compared with patients with AD and control subjects. This was done by computing two-dimensional (2D) sagittal average profiles of the ROIs in each group to describe possible differences in the patterns of atrophy in functionally distinct antero-posterior axis of the structures. This approach is based on the assumption that structure and function in the brain are not independent but that they interact. Hence, the shape of a given structure may also reflect the integrity of the tissue (Van Essen 1997). We thus hypothesized that two different dementias with distinct pathologies, clinical manifestations, and different amounts of MTL damage might display different patterns of atrophy.

Methods and Materials

Subjects and Clinical Assessment

Subjects in this study have been described previously in more detail (Frisoni et al 1999). Given that the present study included an additional FTD patient, the study protocol and characteristics are presented briefly. The study population consisted of 73 subjects of whom 30 were patients with mild to moderate AD (mean age 73 ± 9 years; 23 female subjects, 7 male subjects), 13 patients with FTD (mean age 62 ± 5 years; 3 female subjects, 10 males subjects), and 30 were control subjects (mean age 71 ± 8; 20 female subjects, 10 male subjects) (Table 1). Routine dementia assessment at the Alzheimer's unit (Brescia, Italy) was carried out in all the participants. This included clinical and neurologic examination; comprehensive neuropsychological evaluation, including Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR); laboratory studies including complete blood count, B_{12} and folic acid, thyroid function, and chemistry profile; chest x-ray, ECG, EEG, ^{99}Tc-HMPAO SPECT, and CT. Disease history was questioned from a knowledgeable informant, focusing particularly on symptoms that might help in the diagnostic differentiation of the dementia form, as well as to assess activities of daily living.

The AD patients met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations' criteria for probable AD (McKhann et al 1984). The diagnosis of FTD was made according to the guidelines by the Lund and Manchester Groups (1994). The diagnoses of dementia were substantiated in follow-up evaluations. In SPECT, the FTD patients invariably displayed anterior hypoperfusion, whereas the hypoperfusion in the AD patients tended to be temporoparietal. None of the FTD or AD patients had clinical features of Parkinsonism, motor

neuron disease, or progressive aphasia in the absence of other cognitive or behavioral disturbances. A vascular component was excluded clinically as an absence of sudden onset and focal symptoms, and further by the findings in CT and MRI. A neurologist and a psychologist examined the control subjects. The control group consisted of the patients' relatives (mostly spouses) who did not have any detectable cognitive deficits and who had a negative history of any neurological disease.

Written informed consent was obtained from both cases and control subjects or from their primary caregivers after discussion of risks and benefits of participation. No compensation was provided. The local ethics committee approved the study.

MRI Protocol and Analysis

MRI was performed at the Department of Radiology, University of Verona, Italy, with a 1.5 Tesla scanner (Siemens Magnetom; Erlangen, Germany) using a standard head coil and a T_1-weighted magnetization prepared rapid acquisition gradient echo (TR 10 msec; TE 4 msec; TI 300 msec; flip angle 10°; field of view 250 mm; acquisition 2; matrix 160 × 256), resulting in 128 sagittal images.

Volumetric measurements and analyses were made at the Kuopio University Hospital, Finland. The scans were reconstructed coronally, oriented perpendicular to the intercommissural line. The ROIs were manually traced from contiguous 2.0-mm-thick images by a single tracer, blinded to the subjects' clinical data, using custom-made software for a standard Siemens' work console. The anatomical starting point was the rostral end of the hippocampus when it first appears below the amygdala. The tracing of the hippocampus ended posteriorly in the section where the crura of the fornices depart from the lateral wall of the lateral ventricles (Frisoni et al 1999; Laakso et al 1998). The ERC volumes were traced according to the recent criteria by Insausti et al (1998). In brief, the most anterior slice measured was the one after the appearance of temporal stem, and the last slice was the one where the uncus and gyrus intralimbicus were no longer separable.

Once the ROI has been traced, the software calculates the volume for every structure in mm^3 by computing the number of voxels for each traced image. After the tracing is complete, the software also displays the sagittal (lateral) profile of the measured structure for each subject. This profile is formed from each measured slice (area) displayed on the y-axis and the length (number of slices) on the x-axis. The group profiles were calculated by averaging the profiles for each subject from each of the three groups. Because of the slightly different number of slices between individuals, the volume profile was computed by linear interpolation between separate slices for a relative length of 100%, and the subvolumes were computed for 5% intervals (i.e., the number of ROIs for each subject was transformed to 20 for each subject). This was done by using customized macros written for the statistical software for every given number of slices. The atrophy of regions within the ERC and the hippocampus was explored by subdividing the ROIs into three subregions along their antero-posterior axis (i.e., anterior [35%], medial [40–70%], and posterior [75–100%] subregions).

The intraclass correlation coefficient of the intrarater variability was 0.95 for the hippocampus volumes and 0.90 for the ERC. The coronal intracranial area at the level of the anterior commissure was used for normalization of the volumetric data (Frisoni et al 1999; Laakso et al 1998). For data presentation purposes, the volumes reported here are normalized to the intracranial area according to the following formula: (volume/intracranial area) × 1000.

Statistics

One-way analysis of variance (ANOVA) with the Duncan post hoc analysis was used to compare the means between study groups. Differences of proportions were assessed with chi-square test. The relationship of volumes with gender and age was assessed with multivariate ANOVA with the hippocampal and ERC volumes as dependent variables and gender and age (age less than 69 and 70 years or older) as factors. The results are expressed as mean ± SD. The level of statistical significance of the differences is $p < .05$.

Results

The age difference between the FTD group, the AD group, and the control group was significant ($F = 8.2$, $p < .001$), with the FTD group being younger and differing from both the AD and control groups in the post hoc analysis. There were more male patients among the FTD group were than among either the AD and control groups [$\chi^2(2) = 4.9$, $p < .05$]. The groups did not differ with regard to education. As expected, both the AD group and the FTD group performed significantly worse on the MMSE ($F = 56.7$, $p < .0001$; Table 1) compared with control subjects. In the post hoc analysis, the FTD patients scored significantly worse than the AD patients on the MMSE ($p < .05$). By contrast, the distribution on the CDR scale indicated less severe global dementia in the FTD patients, although the finding was not statistically significant. Memory disturbances and disorientation at onset were more frequent in the AD group, whereas both behavioral, oral, and dietary changes and language disturbances dominated the clinical picture of the FTD patients (data not presented). Disease duration did not differ significantly between the demented groups (30 ± 14 months in FTD vs. 41 ± 25 months in AD). The frequency of subjects carrying the ϵ4 allele in the FTD group (18%) was lower than that of the AD group (50%) and equal to that of the control group [21%; $\chi^2(2) = 6.5$, $p < .05$].

The relationship between the hippocampal and ERC volumes with age in the control group was assessed with correlation and locally weighted regression analyses (data not shown). Neither method found any association between the hippocampal and ERC volumes with age. Furthermore, the relationship of volumes with gender and age was assessed with multivariate ANOVA with the hippocampal and ERC volumes as dependent variables

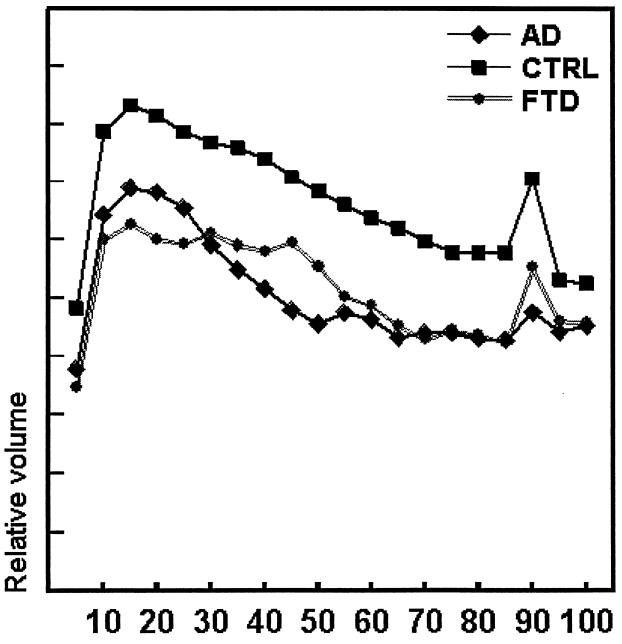
BIOL PSYCHIATRY 1059
2000;47:1056–1063

and gender and age as factors. The main effects and interactions of gender and age never approached significance, which allowed us to continue the following analyses without further controlling for the effects of age and gender.

The normalized volumes of the hippocampi and ERC are displayed on Table 2. Both the hippocampal (right, $F = 22.6$; left, $F = 16.7$) and ERC (right, $F = 9.7$; left, $F = 13.6$) volumes were smaller in the FTD and AD patients compared with the control subjects ($p < .0001$). The patients with FTD had hippocampal volumes intermediate between the control subjects and patients with AD. On the right, the difference reached the level of significance ($p < .05$) between all the groups in the Duncan post hoc analysis. The volumes of ERC were similarly atrophied in the patients with FTD and AD.

The absolute lengths (number of 2.0-mm-thick slices traced) of the structures are also displayed in Table 2. There were no significant differences on the length of the structures between the groups except for the right ERC, which was significantly longer in the control subjects ($F = 4.0$, $p < .05$). The absolute difference in length between the structures and for each group, however, was always less than 1 slice (2 mm).

The sagittal profiles for each structure are displayed in Figures 1–4. Figure 1 shows the topography of the right ERC. Both the patient groups differed from the control group but not from each other at the anterior 70th percentiles. In the posterior subregion on the right, both the patient groups differed from the control group, with the AD patients also having significantly smaller regional volumes than the FTD patients. On the left, both the patient groups differed from the control group throughout the ERC, but not from each other (Figure 2). The profile of the right hippocampus is shown in Figure 3. On the anterior 35th percentile, both the patient groups differed from the control group; on the medial subregion only the patients with AD differed from the control group. In the posterior subregion, the three groups did not differ significantly from each other, although the finding approached significance ($p = .07$). It should be noted, however, that the control and FTD groups had identical volumes in the posterior subregion. On the left (Figure 4) the results were similar; on the anterior subregion, both the patient groups differed from the control group, but not from each other, and on the medial subregion, only the patients with AD differed from the control subjects. In the posterior subregion, the patients with FTD differed significantly from the control group, and the patients with AD differed significantly from both the control subjects and the patients with FTD.



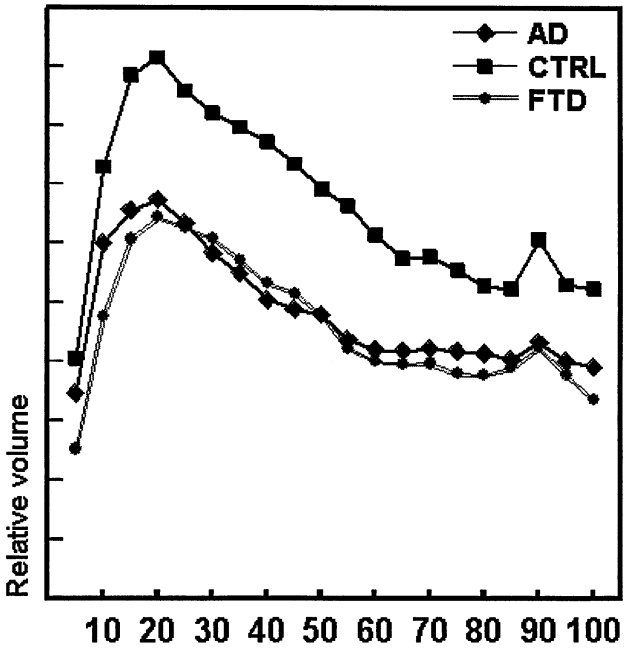
	CTRL	FTD	AD	ANOVA
0–35%	524 ± 143	398 ± 147*	419 ± 146*	$F = 5.3$, $p = .007$
40–70%	466 ± 115	361 ± 141*	327 ± 115*	$F = 10.6$, $p < .0001$
75–100%	351 ± 139	279 ± 120*	268 ± 111**	$F = 3.6$, $p = .03$

Figure 1. Profiles and the regional volumes of the right entorhinal cortex. The y axis displays regional volume at given percentile of relative length (x axis) in percentiles. AD, Alzheimer's disease; CTRL, control subjects; FTD, frontotemporal dementia; ANOVA, analysis of variance. *Groups significantly different from control subjects at the level of $p < .05$ in the post hoc analysis. **Groups significantly different from control subjects at the level of $p < .01$ in the post hoc analysis.

Table 2. Descriptive Results—Normalized Volumes of the Entorhinal Cortices and the Hippocampi and Their Absolute Lengths (Number in 2.0-mm-Thick Slices)

	C	FTD	AD
Right hippocampus			
Volume	149.6 ± 24.5	121.7 ± 33.4[a]	101.8 ± 27.9[b]
Length	16.7 ± 1.5	16.4 ± 1.0	16.2 ± 1.7
Left hippocampus			
Volume	137.6 ± 23.6	115.3 ± 30.9[a]	99.5 ± 25.1[a]
Length	16.9 ± 1.7	16.3 ± 0.9	16.4 ± 1.8
Right entorhinal cortex			
Volume	86.2 ± 21.9	63.2 ± 24.6[a]	62.9 ± 21.2[a]
Length	12.8 ± 1.1	12.0 ± 1.0[a]	12.1 ± 1.2[a]
Left entorhinal cortex			
Volume	81.3 ± 20.0	55.0 ± 21.4[a]	58.6 ± 17.5[a]
Length	12.1 ± 1.0	11.6 ± 0.8	11.8 ± 1.4

C, control subjects; FTD, frontotemporal dementia; AD, Alzheimer's disease.
[a]Significantly different from control subjects at the level of $p < .05$ in the Duncan post hoc analysis.
[b]Significantly different from control subjects at the level of $p < .01$ in the Duncan post hoc analysis.



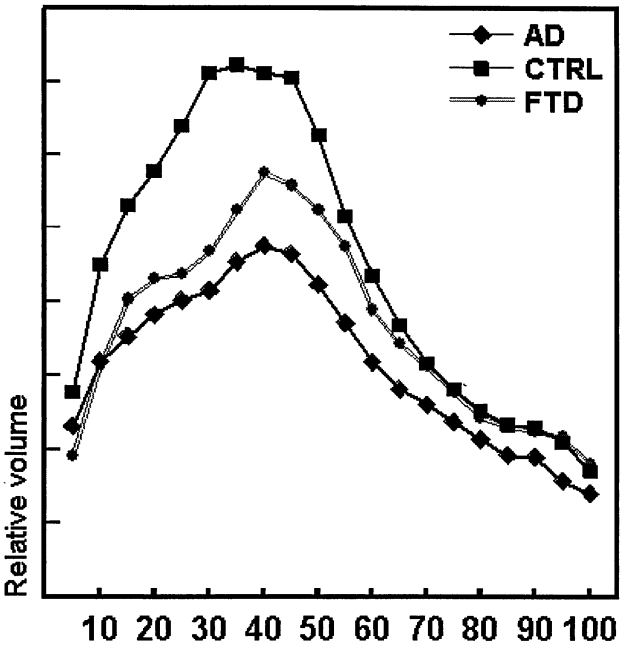
	CTRL	FTD	AD	ANOVA
0–35%	542 ± 170	380 ± 132*	405 ± 106*	$F = 9.6, p < .0001$
40–70%	464 ± 110	316 ± 145*	318 ± 110*	$F = 13.9, p < .0001$
75–100%	328 ± 129	230 ± 109*	247 ± 88*	$F = 5.5, p = .006$

Figure 2. Profiles and the regional volumes of the left entorhinal cortex. The y axis displays regional volume at given percentile of relative length (x axis) in percentiles. AD, Alzheimer's disease; CTRL, control subjects; FTD, frontotemporal dementia; ANOVA, analysis of variance. *Groups significantly different from control subjects at the level of $p < .05$ in the post hoc analysis.

Discussion

In this study, we used volumetric MRI to form 2D topographic models of the hippocampus and the ERC in controls subjects, patients with AD, and patients with FTD. Our previous quantitative finding that both the hippocampus and ERC are atrophic in both the AD and FTD groups compared with the control group were repeated with an additional FTD patient (Frisoni et al 1999). In short, hippocampal atrophy in FTD was less severe than in AD, whereas the atrophy of the ERC was of equal degree in both of the patient groups. The approach of this paper, however, is entirely different from the previous study, and the scope of it reaches beyond the quantitative terms. Judging by the profiles, we suggest that hippocampal atrophy in FTD is weighted in the anterior part of the hippocampus, with much less atrophy evident posteriorly. Particularly on the right side, the posterior subregional volumes are identical in the control and FTD groups. The ERC volumes displayed identical atrophy quantitatively and topographically in both the patient groups, with the exception of the posterior ERC on the right, which was significantly more atrophied in the patients with AD.

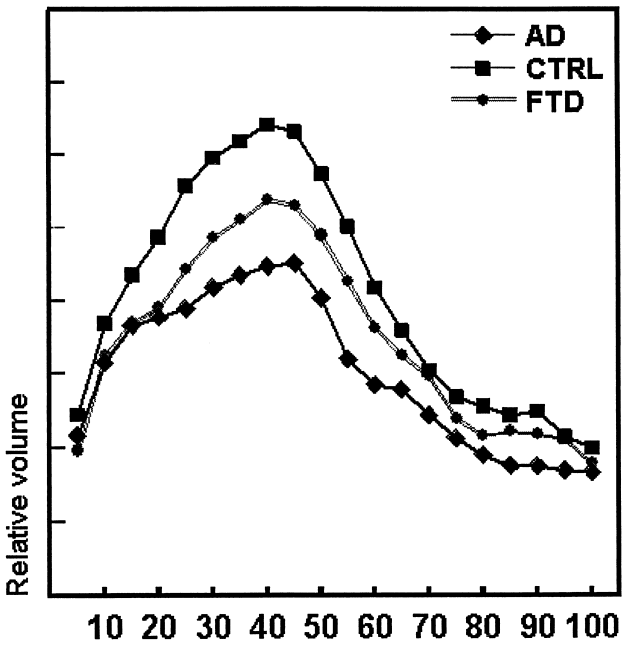
The question about the pathology underlying the observed finding is intriguing. In AD, the pathology of the hippocampus-entorhinal complex is well established (Braak and Braak 1991; Hyman et al 1984), whereas the neuroanatomical or neuropathological al substrates for the current finding in FTD require further exploration. Although neuropathological data on FTDs with regard to the hippocampus have suggested various patterns of atrophy, several studies seem to support the view for lesser damage, ranging from minor involvement to no involvement (Bergmann et al 1992; Brun 1993; Filley et al 1994; Kinoshita et al 1997; Nagaoka et al 1995). There are fewer data on the ERC involvement in FTD. There is, however, some data to support these findings. In a recent study, spheroidical enlargements of presynaptic terminals, suggestive of a retrograde degenerative process in FTD were found in the hippocampus, with the spheroids being most abundant in a region rich in perforant pathway terminals (Zhou et al 1998). The ERC was reported to be substantially spared.



	CTRL	FTD	AD	ANOVA
0–35%	783 ± 138	555 ± 137*	512 ± 163*	$F = 26.9, p < .0001$
40–70%	737 ± 194	637 ± 204	520 ± 170*	$F = 10.2, p < .0001$
75–100%	276 ± 96	276 ± 103	227 ± 69	$F = 2.8, p < .07$

Figure 3. Profiles and the regional volumes of the right hippocampus. The y axis displays regional volume at given percentile of relative length (x axis) in percentiles. AD, Alzheimer's disease; CTRL, control subjects; FTD, frontotemporal dementia; ANOVA, analysis of variance. *Groups significantly different from control subjects at the level of $p < .05$ in the post hoc analysis.

BIOL PSYCHIATRY 1061
2000;47:1056–1063



	CTRL	FTD	AD	ANOVA
0–35%	663 ± 105	547 ± 148*	504 ± 159*	$F = 10.3$, $p < .0001$
40–70%	687 ± 189	596 ± 159	486 ± 128*	$F = 11.8$, $p < .0001$
75–100%	287 ± 115	258 ± 96*	219 ± 58**	$F = 3.9$, $p = .03$

Figure 4. Profiles and the regional volumes of the left hippocampus. The y axis displays regional volume at given percentile of relative length (x axis) in percentiles. AD, Alzheimer's disease; CTRL, control subjects; FTD, frontotemporal dementia; ANOVA, analysis of variance. *Groups significantly different from control subjects at the level of $p < .05$ in the post hoc analysis. **Groups significantly different from control subjects at the level of $p < .01$ in the post hoc analysis.

In another study on chromosome 17–linked FTD, there was damage of the ERC, with the hippocampus being substantially spared except for degeneration of those regions receiving input from the perforant pathway. The finding was considered secondary to entorhinal nerve cell loss (Sima et al 1996).

Indeed, the hippocampus has its major cortical input from the ERC. The ERC serves as a source of excitatory input, the perforant pathway, which projects to the dentate gyrus, CA1, CA3, the subiculum, and beyond to further internal projections. This results in the ventral and dorsal parts of the hippocampus selectively receiving different kinds of input (Witter and Groenewegen 1992). One possible explanation for the findings, therefore, is that anterior temporal pathology in FTD might lead to direct involvement of the ERC. Alternatively, there may be more extensive disruption of various cortico-cortical and cortico-basal circuits, resulting in damage of the ERC, and to subsequent bystander damage to the hippocampus. Given the neuropathological data suggesting sparing of the hippocampus in FTD, this observed pattern of atrophy may also be nonprogressive. In this way, FTD differs from AD, where these regions are not only the first ones to be affected, but also show progressive deterioration and are among the most severely degenerated regions at the end-stage disease (Braak and Braak 1991; Hyman et al 1984).

The substantial sparing of the posterior part of the hippocampus in FTD also implies clinical correlations in FTD. The hippocampus has not only connectional but also functional differences along its longitudinal axis (Colombo et al 1998; Moser et al 1993; Schacter and Wagner 1999). The posterior part of the hippocampus has been suggested to subserve memory encoding (Schacter and Wagner 1999), as well as visuospatial memory (Moser et al 1993). Notably, these functions are considered to be substantially spared in FTD. By contrast, deficits in the more anterior parts of the temporal lobe, such as the amygdala, might be associated with the behavioral or language disturbances prominent in FTD.

Some possible caveats of this study deserve consideration. First, age, gender, and disease severity were different between the patients with FTD and those with AD. The patients with AD and the control patients were significantly older than the FTD patients. This, however, takes place by default, if one wants to match the groups with disease duration or severity, because the onset of FTD is typically younger. In fact, the younger age of our FTD patients may favor correct diagnosis of true FTD because frontal lobe syndromes in the very elderly are common, but only a minority actually has primary FTD (Gislason et al 1998). Although the MMSE was indicative of greater severity in the FTD group, the other indicators (such as duration, CDR, and basic and instrumental disability) pointed toward no difference or slightly greater severity in the AD group. Indeed, because the MMSE is highly dependent on the integrity of language function (Goldblum et al 1994), it may not serve as a good instrument for measurement of global severity in conditions such as FTD, in which language disturbances are particularly dominant.

With regard to age, neither the hippocampal or ERC volumes were correlated with age in the group of control subjects in this or other larger studies by our group (Insausti et al 1998; Laakso et al 1998) or others (DeCarli et al 1994; Sullivan et al 1995). In agreement with previous studies, the hippocampal and the ERC volumes did not differ between control men and women after adjustment for head size (Insausti et al 1998; Laakso et al 1998). The entorhinal cortex on the right was significantly longer in control subjects, but in absolute terms never exceeded 2.0 mm. There were no differences in the hippocampal lengths between the groups. Nonetheless, because no pathologic specimen or genetic data on chro-

mosome 17–linked anomalies were available from any of the subjects, possible conceptual bias related with colorful nosology of FTD cannot be excluded. Differentiation of subtypes of FTD on clinical grounds is difficult, if not impossible. Therefore, we cannot rule out the possible impact of different variants of FTD or the possibility of rare "focal AD," presenting with behavioral and language disturbances and sparing of memory early in the course of disease (Jagust et al 1990). Nonetheless, SPECT perfusion patterns do not indicate any marked heterogeneity of FTD in this material in that all patients with FTD showed marked frontal hypoperfusion on SPECT scans (Frisoni et al 1995). Moreover, the neuropsychologic pattern also has been studied in patients with FTD and found to be as expected from study of the literature (marked disturbance of language production with sparing of nonverbal learning; Frisoni et al 1995). The absence of Parkinsonism or features of motor neuron disease should also reduce heterogeneity. None of the subjects were known to have an autosomal-dominant mode of inheritance, and the frequency of apolipoprotein E ϵ4 in FTD did not differ from control subjects but was significantly lower than in patients with AD (Geschwind et al 1998).

Another conceptual factor is related with anatomic and functional division of the ROIs. Whereas the hippocampus can be divided to three subregions—the head, the body, and the tail, which coarsely correspond the subdivisions in the present study—no such distinction exists for the ERC. That, however, may be beside the point. Of relevance here is the fact that morphometry can be utilized to study hippocampus, and this approach may reveal distinctive groupwise patterns between the study groups, as is the case in this study. The subdivision to three regions rather should be considered as a means of presentation of the data. By using the method, regional differences could be calculated for every fifth percentile, if necessary.

These data provide novel insight into the pattern of medial temporal lobe damage in FTD. In conclusion, both the hippocampus and ERC are atrophic in AD and FTD. The extent and pattern of atrophy of the ERC is virtually similar in both of the dementias. By contrast, the hippocampal atrophy in FTD is less severe than in AD and appears to be attributable to atrophy located mainly in the anterior hippocampus with relative sparing of the postrior part. It is possible that the observed pattern of hippocampal damage is secondary to entorhinal pathology. Further, it is suggested that straightforward morphometric approach provides valuable additional information compared with conventional quantitative MRI. It appears possible that structural imaging may identify different patterns of atrophy, and this can be utilized to better characterize various primary degenerative dementias with different underlying pathologies. This approach may provide a means to find substrates to different patterns of structure-function relationship or functional impairment in vivo.

This study was supported by an EVO grant from Kuopio University Hospital and by the Research Council for Health of the Academy of Finland. The authors thank E. Koivisto for help with the preparation of the figures and G. Puppini and A. Gassan with the management of the image files. T. Metitieri and A. Pezzini helped with the data collection, and Dr Giuliano Binetti provided the neuropsychologic data.

References

Bergmann M, Kuchelmeister K, Schmid KW, Kretzschmar HA, Schröder R (1992): Different variants of frontotemporal dementia: A neuropathological al and immunohistochemical study. *Acta Neuropathol* 92:170–179.

Braak H, Braak, E (1991): Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 82:239–259.

Brun A (1987): Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. *Arch Gerontol Geriatr* 6:193–208.

Brun A (1993): Frontal lobe degeneration of non-Alzheimer type revisited. *Dementia* 4:126–131.

Colombo M, Fernandez T, Nakamura K, Gross CG (1998): Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. *J Neurophysiol* 80:1002–1005.

Csernansky JG, Joshi S, Wang L, Haller JW, Gado M, Miller JP, et al (1998): Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proc Natl Acad Sci U S A* 95:11406–11411.

DeCarli C, Murphy DGM, Gillette JA, Haxby JV, Teichberg D, Schapiro MB, Horwitz B (1994): Lack of age-related differences in temporal lobe volume of very healthy adults. *Am J Neuroradiol* 15:689–696.

Filley CM, Kleinschmidt-De Masters BK, Gross KF (1994): Non-Alzheimer fronto-temporal degenerative dementia. A neurobehavioral and pathologic study. *Clin Neuropathol* 13: 109–116.

Frisoni GB, Laakso MP, Beltramello A, Geroldi C, Bianchetti A, Soininen H, Trabucchi M (1999): Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology* 52:91–100.

Frisoni GB, Pizzolato G, Geroldi C, Rossato A, Bianchetti A, Trabucchi M (1995): Dementia of the frontal type: Neuropsychological and [^{99}Tc]-HM-PAO SPET features. *J Geriatr Psychiatry Neurol* 8:42–48.

Geschwind D, Karrim J, Nelson SF, Miller B (1998): The apolipoprotein E ϵ4 allele is not a significant risk factor for frontotemporal dementia. *Ann Neurol* 44:134–138.

Gislason T, Larsson L, Sjögren M, Skoog I (1998): A population-based study on the prevalence of frontal lobe dementia in 85-year olds (abstract). *Neurobiol Aging* 19(suppl 4):S309.

Goldblum M-C, Tzortzis C, Michot JL, Panisset M, Boller F (1994): Language impairment and rate of cognitive decline in Alzheimer's disease. *Dementia* 5:334–338.

Gómez-Isla T, Price JL, McKeel DW, Morris JC, Growdon JH, Hyman BT (1996): Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci* 16:4491–4500.

Hyman BT, Damasio AR, Van Hoesen GW, Barnes CL (1984): Alzheimer's disease: Cell-specific pathology isolates the hippocampal formation. *Science* 225:1168–1170.

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, et al (1998): MR imaging volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *Am J Neuroradiol* 19:659–671.

Jack CR Jr, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, et al (1997): Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 49:786–794.

Jagust WJ, Davies P, Tiller-Borcich JK, Reed BR (1990): Focal Alzheimer's disease. *Neurology* 40:14–19.

Kennedy DN, Lange N, Makris N, Bates J, Meyer J, Caviness VS Jr (1998): Gyri of the human neocortex: an MRI-based analysis of volumes and variance. *Cereb Cortex* 8:372–384.

Kinoshita A, Tomimoto H, Suenaga T, Akiguchi I, Kimura J (1997): Ubiquitin-related cytoskeletal abnormality in frontotemporal dementia: Immunohistochemical and immunoelectron microscope studies. *Acta Neuropathol* 94:67–72.

Knopman DS, Mastri AR, Frey WH II, Sung JH, Rustan T (1990): Dementia lacking distinctive histologic features: A common non-Alzheimer degenerative dementia. *Neurology* 40:251–256.

Laakso MP, Soininen H, Partanen K, Lehtovirta M, Hallikainen M, Hänninen T, et al (1998): MRI of the hippocampus in Alzheimer's disease: Sensitivity, specificity and analysis of the incorrectly classified subjects. *Neurobiol Aging* 19:23–31.

Lund and Manchester Groups (1994): Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 57:886–896.

McKhann G, Drachman D, Folstein MF, Katzman R, Price D, Stadlan EM (1984): Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group. *Neurology* 34:939–944.

Mega MS, Thompson PM, Cummings JL, Back CL, Xu ML, Zohoori S, et al (1998): Sulcal variability in the Alzheimer's brain: Correlations with cognition. *Neurology* 50:145–151.

Moser E, Moser MB, Andersen P (1993): Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *J Neurosci* 13:3916–3925.

Nagaoka S, Arai H, Iwamoto N, Ohwada J, Ichimiya Y, Nakamura M, Inoue R (1995): A juvenile case of frontotemporal dementia: Neurochemical and neuropathological investigations. *Prog Neuropsychopharmacol Biol Psychiatry* 19: 1251–1261.

Schacter DL, Wagner AD (1999): Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9:7–24.

Sima AAF, Defendini R, Keohane C, D'Amato C, Foster NL, Parchi P, et al (1996): The neuropathology of chromosome 17-linked dementia. *Ann Neurol* 39:734–743.

Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A (1995): Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. *Neurobiol Aging* 6:591–606.

Van Essen DC (1997): A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 385:313–318.

Witter MP, Groenewegen HJ (1992): Organizational principles of hippocampal connections. In: Trimble MR, Bolwig TG, editors. *The Temporal Lobes and the Limbic System.* Petersfield, UK: Wrightson Biomedical Publishing, 37–60.

Zhou L, Miller BL, McDaniel CH, Kelly L, Kim OJ, Miller CA (1998): Frontotemporal dementia: Neuropil spheroids and presynaptic terminal degeneration. *Ann Neurol* 44:99–109.