

Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease

G.B. Frisoni, MD; M.P. Laakso, MD, PhD; A. Beltramello, MD; C. Geroldi, MD, PhD; A. Bianchetti, MD; H. Soininen, MD, PhD; and M. Trabucchi, MD

Article abstract—*Objective:* To describe atrophic changes of the hippocampus and entorhinal cortex in frontotemporal dementia (FTD) and compare them with those of AD. *Background:* The medial temporal lobe shows atrophic changes early in the course of AD, but whether these changes are specific to AD or occur in other degenerative dementias, and to what extent, is unclear. *Methods:* The authors measured the volumes of the left and right hippocampus and entorhinal cortex from MR images (1.5 T, 2-mm-thick slices) in 12 patients with FTD, 30 with AD, and 30 elderly control subjects. *Results:* In FTD patients, the left and right hippocampus (16% and 21% tissue loss) and the entorhinal cortex (28% and 27% loss) were more atrophic than the control subjects. Atrophy of the hippocampus in FTD was less severe than in AD, but atrophy of the entorhinal cortex was equally severe. Greater hippocampal and entorhinal cortex atrophy was present in the most severe patients in both groups (as high as a 49% tissue loss). The sensitivity of the hippocampus and the entorhinal cortex to discriminate FTD patients from control subjects was low (49% and 52%, respectively; specificity set at 90%), whereas hippocampal volumes could better differentiate AD patients from control subjects (80% sensitivity). *Conclusions:* At variance with AD, detectable in vivo atrophy of the hippocampus might not be an early event in FTD. Differential patterns of atrophy might help in the diagnostic process of the degenerative dementias.

NEUROLOGY 1999;52:91–100

The volumetric measurement of brain structures with MRI is being investigated intensively in a number of brain diseases that fail to show characteristic features on traditional MR examinations. In the field of the degenerative dementias, this work will hopefully enhance the accuracy of the management of the neurologic patient by increasing diagnostic accuracy, by helping to monitor disease progression, and by identifying responders to drug treatment. This effort is made even more relevant by the lack of biological markers that might be of diagnostic or prognostic value in most dementing disorders. Specifically, the clinical differentiation of the degenerative dementias is a particularly difficult task.

Early volumetric work showed that volumetric measurements of the hippocampus could distinguish AD patients reliably from noncognitively impaired elderly people.^{1,2} However, it became clear with additional research that hippocampal atrophy was not specific for AD, but could be found in other degenerative dementias.^{3–6}

Some observations indicate that patterns of atrophy in some brain areas rather than atrophy in one single area might be distinctive of brain cognitive disorders in the elderly. In patients with AD and

late-onset depression, Pantel et al.⁷ showed that, although AD had significant shrinkage of the whole brain, amygdala–hippocampal complex, and frontal and temporal lobes compared with nondepressed, nondemented control subjects, depressed patients had shrinkage of the whole brain but preservation of amygdala–hippocampal and lobar volumes. Double et al.⁵ studied idiopathic PD and Lewy body dementia and found that medial temporal atrophy was present in both groups, but marked frontal lobe atrophy was present only in Lewy body dementia. However, data are still scanty on atrophic patterns in the most common degenerative dementias.

Frontotemporal dementia (FTD) is a primary degenerative dementia that is recognizably distinct from AD, and its prevalence ranges between 2 and 20% of all the degenerative dementias.^{8–10} Its clinical features are characteristic and comprise prominent behavioral disturbances and language deficits with a late-adult or senile onset and a progressive course. Unlike AD, episodic memory and visuospatial functions are notably spared.^{11–13} Histopathologically, unspecific degenerative change of the anterior regions of the frontal and temporal lobes, such as microvacuolization, gliosis, and neuronal loss, can be demonstrated.^{14,15}

From the IRCCS San Giovanni di Dio–FBF (Drs. Frisoni, Geroldi, Bianchetti, and Trabucchi), Brescia, Italy; the Departments of Neurology (Drs. Laakso and Soininen) and Clinical Radiology (Dr. Laakso), Kuopio University Hospital, Kuopio, Finland; and the Institute of Radiology (Dr. Beltramello), University of Verona, Ospedale Borgo Roma, Verona, Italy.

This work was written while G.B.F. was on a sabbatical at the Stockholm Gerontology Research Center, Department of Clinical Neuroscience and Family Medicine, Karolinska Institute (Head, Prof. Bengt Winblad).

Received May 15, 1998. Accepted in final form September 19, 1998.

Address correspondence and reprint requests to Dr. Giovanni B. Frisoni, Alzheimer's Unit, IRCCS San Giovanni di Dio, FBF, via Pilastroni 4, I-25123 Brescia, Italy; e-mail: frisoni@master.cci.unibs.it

Atrophic changes on gross pathologic examination are variable, but some authors^{9,16,17} suggest that they might be from absent to moderate. Nevertheless, we have shown recently⁴ that atrophic changes of the medial temporal lobe region can be appreciated with quantitative measures of atrophy, and that greater frontal atrophy, sparing of the parahippocampal region, and asymmetric enlargement of the temporal horn (more marked to the left) suggest that the pattern of atrophy of FTD patients is distinct from that of AD patients. However, the use of linear measures to estimate atrophy prevented the direct assessment of some key regions such as the hippocampus and the entorhinal cortex (ERC). Pathologic and imaging studies indicate that these regions are affected early in the disease process of AD,^{1,18-20} and recent evidence suggests an involvement also in FTD.^{10,21-25} In fact, atrophy of the hippocampus in FTD has been reported at autopsy,^{8,14,15} and pathologic changes in the ERC have been reported in cases of FTD,²² FTD with motor neuron disease,²¹ and FTD associated with chromosome 17.²³ However, changes of the hippocampus and the ERC have never been documented *in vivo* in FTD patients.

The aim of this study is to expand the description of atrophy of FTD, which we carried out previously with linear measures, by measuring volumes of the hippocampus and the ERC in FTD patients and to compare it with that of AD patients and normal elderly control subjects.

Methods. *Patients and clinical assessment.* Patients and normal elders in this study have been described previously^{4,20} in reports on linear measures of atrophy in the degenerative dementias. Here we summarize the assessment protocol.

The subjects with dementia were outpatients seen at the Alzheimer's Unit, Brescia, Italy. Routine dementia assessment and workup was carried out in patients. History was taken from a knowledgeable informant (usually the patient's spouse), and was particularly focused on those symptoms that might help in the diagnostic differentiation of the dementia forms (implicit and explicit memory, language and executive functions, behavioral disturbances, disability in daily activities, hallucinations and other psychiatric symptoms, and falls). Laboratory studies included complete blood count, chemistry profile, chest radiograph, thyroid function, B₁₂ and folic acid, EKG, EEG, and CT. Neurologic examination (including elicitation of primitive reflexes such as grasping, sucking, palmonental, and snout) was performed by a neurologist, and physical examination was performed by a geriatrician. Whenever feasible, patients underwent a comprehensive neuropsychological battery aimed at detecting early cognitive impairment, the results of which have been described elsewhere in greater detail.⁴

The diagnosis of FTD was made based on clinical grounds after clinical and pathologic descriptions¹¹ and guidelines.^{12,13} These suggest that FTD is a progressive condition characterized by behavioral and often language disturbances early in the disease course. Behavioral disturbances include disinhibition, lack of insight and judgment, emotional unconcern, loss of social graces,

hyperphagia, and obsessiveness, whereas the language deficit involves the anterior (productive) component with reduction of spontaneous speech output and echolalia. Learning abilities and topographic orientation are spared until the very late stages of the disease. Functional dependency develops later than in AD, and when present is due more to behavioral rather than memory and cognitive disturbances.²⁶ A vascular component was excluded on the basis of CT and MRI.²⁶ The diagnosis was confirmed by brain SPECT with ^{99m}Tc = hexamethylpropylene amine oxine, invariably showing anterior hypoperfusion.²⁶ It should be emphasized that anterior hypoperfusion on SPECT was necessary but by no means sufficient to make the diagnosis of FTD. Four patients with very severe frontal or temporal atrophy on MRI, suggestive of Pick's disease,²⁷ and two patients with progressive aphasia in the absence of other cognitive and behavioral disturbances were seen during the enrollment period and were excluded from the current study. The diagnosis of FTD was confirmed on follow-up evaluations. Although some behavioral disturbances (such as disinhibition, hyperphagia, and obsessiveness) tended to disappear as the disease progressed, and others (such as apathy and mutism) increased, on follow-up evaluation all patients still had a marked sparing of memory, topographic orientation, or daily function.

AD patients met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD.²⁸ None had clinical features suggestive of dementia of the Lewy Body type (hallucinations, parkinsonism, sensitivity to neuroleptic medication, fluctuations, and falls).

A positive family history of dementia was present when a first-degree relative had shown progressive cognitive deterioration consistent with dementia. Although a formal behavioral assessment was not carried out in all patients at the time of MRI, Cummings' Neuropsychiatric Inventory was administered to some patients at a later time,²⁹ showing that FTD and AD patients had distinct behavioral profiles that were consistent with recent descriptions.¹³ The Italian version of Folstein's Mini-Mental State Examination (MMSE) was used to assess cognition.³⁰ Language abilities were evaluated with the Controlled Oral Word Association Test, which require the patient to say as many words as possible starting with the letters "p," "f," and "l" in 3 minutes (1 minute for each letter). Disease duration was computed from the estimated onset to the date of MRI. The estimated onset was assessed from informants and defined as the time of the first appearance of memory, behavioral, language, or other symptoms that could be due to degenerative brain disease. Overall dementia severity was assessed with the Clinical Dementia Rating scale (CDR),³¹ which compounds information on memory disturbances and daily function. Information on basic (bathing, dressing, grooming, walking, feeding, and continence) and instrumental (using the telephone, shopping, cooking, doing housework, doing laundry, using public transportation, taking drugs, and handling finances) activities of daily living was taken from a proxy informant.

Control subjects were patients' relatives (mostly spouses) without detectable cognitive deficit. They had a negative history of neurologic disease, although some reported mild subjective memory problems that did not re-

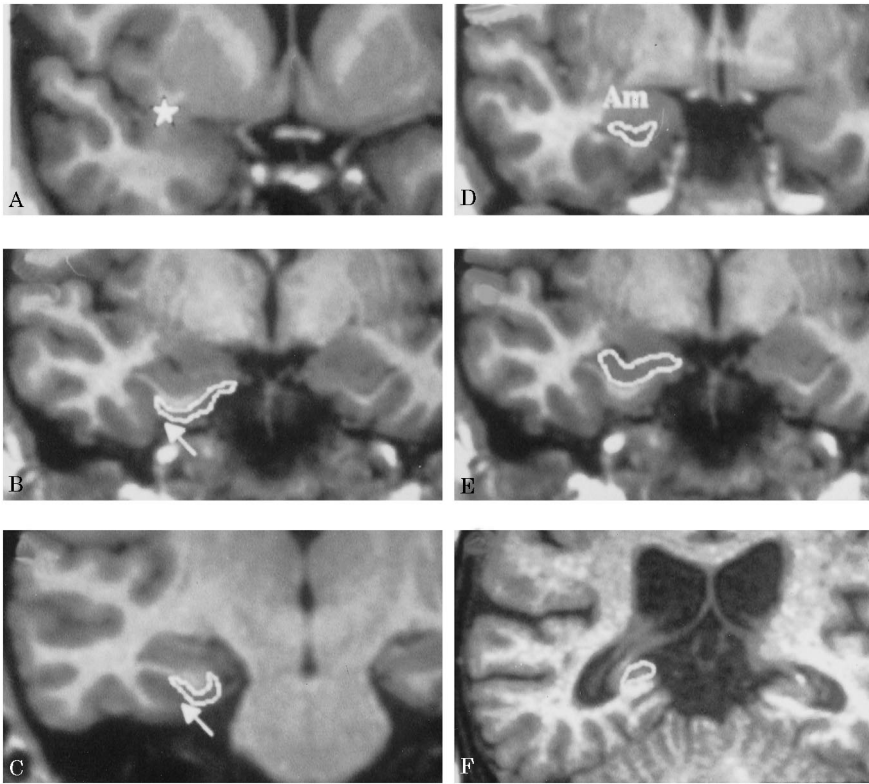


Figure. Tracing of the entorhinal cortex and hippocampus. (A–C) The entorhinal cortex (ERC). (A) The temporal lobe gets attached to the rest of the brain by the limen insula (star). This slice is a reference point for ERC tracings starting from the following posterior slice (not shown). (B) An example of an ERC tracing. The lateral ERC boundary—the border between the entorhinal and perirhinal cortices—is at the midpoint of the medial bank of the collateral sulcus (solid arrow). The medial boundary is at the level of the sulcus semianularis (open arrow). (C) Presented is the slice in which the uncus and gyrus intralimbicus can no longer be separated, which is the last slice in which the ERC is traced. (D–F) The hippocampus. (D) Presented is the most anterior slice in which the hippocampus can be appreciated to the right, just below the amygdala (Am). (E) An example of a hippocampal tracing (same slice as in C). (F) Presented is the last slice in which the hippocampus is traced. The crus of the fornix departing from the

lateral wall of the lateral ventricle on the right side can still be appreciated. Top to bottom: anterior to posterior.

sult in impairment of daily activities. All were administered the MMSE and were judged not to be demented by a neurologist and a psychologist involved in the evaluation of the patients. Because the Controlled Oral Word Association Test was not available for these subjects, normal values were considered those of a group of 66 relatives who had been enrolled in a normative study of a neuropsychological battery for the assessment of dementia.³² Their age was 68 ± 5 years, women comprised 50% of the cohort, and educational background was 9 ± 4 years of schooling.

Apolipoprotein E phenotyping was performed on patients and control subjects with isoelectric focusing on delipidated plasma samples.

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

Of the original 14 FTD patients,⁴ 1 had been scanned with spin-echo sequences, and volumetrics could not be carried out, and 1 had not deteriorated after 3 years of follow-up. The remaining 12 FTD patients were followed clinically from a minimum of 2 years to a maximum of 4.5 years, and diagnosis of FTD was confirmed at follow-up on the basis of deterioration of language and behavior with sparing of visuospatial abilities. Telephone follow-up after an average of 3.5 years showed that 4 patients had died and the remaining 8 were severely disabled (all had lost four or more basic activities of daily living). These 12 FTD patients were included in the current study. Thirty of the original 43 AD patients and 30 of the 31 control subjects had images suitable for volumetric analysis.

Volumetrics. MRI was performed at the Radiology Department, University of Verona, with a 1.5-T unit (Magnetom; Siemens GmbH, Erlangen, Germany) and a standard head coil. A gradient-echo three-dimensional technique was used for image acquisition (repetition time, 10 msec; echo time, 4 msec; inversion time, 300 msec; flip angle, 10 deg; field of view, 250 mm; acquisitions, 2; matrix, 160 × 256). Total acquisition time was 7:40 minutes.

Volumetric analysis was made by a single rater (M.P.L.), who was blind to the subject's diagnosis and clinical data. The regions of interest (ROIs) were traced manually from contiguous coronal 2.0-mm-thick T1-weighted images oriented perpendicular to a midsagittal line drawn through the anterior and posterior commissures. Tracing proceeded from anterior to posterior for both the hippocampus and the ERC. The volume of the hippocampus (considered as dentate gyrus, hippocampus proper, and the subicular complex) was measured starting from its appearance below the amygdala (figure). The uncus portion of the rostral hippocampus that is located ventral to the caudal amygdala was included in the hippocampus. The tracing ended posteriorly in the section where the crura of the fornices depart from the lateral wall of the lateral ventricles (see the figure).³ The entorhinal volumes were traced according to the criteria of Insausti et al.,³³ with minor modifications. The first slice measured was the one after the appearance of limen insula when the temporal lobe can be first appreciated to be attached to the rest of the brain when proceeding from the anterior position (see the figure). The last slice was the one in which the uncus and gyrus intralimbicus could no longer be appreciated (see the figure).

When the ROIs had been traced, the volumes were cal-

culated in cubic millimeters by computing the number of voxels within the traced images using specifically developed software for a standard work console. The reported intrarater variability for the measurements is 6.7% for the hippocampus³ and 7.4% for the ERC.³³ The intracranial area (in square millimeters) on a coronal section at the level of the anterior commissure was measured and used for normalization of the volumetric data. For data presentation purposes, the volumes reported herein are normalized to the intracranial area according to the formula: (volume/intracranial area) \times 100.³ The right, left, and smallest volumes were considered, the smallest being the most atrophic between the right and the left sides for each subject. Volume loss was defined as the percentage difference of patients' volumes with respect to the mean of control subjects (set at 100).

Statistical analysis. Statistical analysis was performed with SPSS, release 5.1 (SPSS Inc., Chicago, IL). The significance of intergroup or intragroup differences of continuous variables was assessed with the *t*-test or analysis of variance (ANOVA) for independent samples. Differences of proportions were assessed with the chi-square test.

The *t*-test for repeated measures was used to assess intragroup differences of continuous variables (volumes \times side). A test for trend was used to assess the significance of increasing atrophy among groups. This was carried out in linear regression models in which atrophy was the dependent variable and group (coded as a three-level continuous variable) was the independent variable. Group coding (0, 1, and 2) mirrored the order of increasing atrophy indicated by mean volumes. Adjustment was made in the regression model for age, gender, and dementia severity (CDR).

The effect of diagnosis (FTD versus AD) and disease severity (CDR score, 0.5/1 versus 2/3), and their interaction on brain volumes was assessed using ANOVA. The significance of the interaction was tested in a full factorial model (i.e., including the two main effects of diagnosis and disease severity, and their interaction). If the interaction term proved not to be significant, a model with main effects only was built.

The critical level for statistical significance was set at $p < 0.05$ for all tests.

Discriminant analysis was used to identify the variable best discriminating patients from control subjects and to compute the accuracy of the discrimination. Discriminant models were built separately for the hippocampus and the ERC, and for FTD and AD patients versus control subjects. Right, left, and smallest volumes were entered as independent variables and tested with a stepwise method for independent contribution to separate patients from control subjects. Entering of variables was based on the smallest Wilks' lambda of the discriminant function and on F-to-enter for Wilks' lambda > 3.84 . Removal of variables was based on F-to-remove values for Wilks' lambda < 2.71 .

The variable thus identified was used to compute its sensitivity to detect FTD or AD patients with specificity set at 90% (i.e., a fixed 10% of control subjects were allowed to be misclassified as patients). This was carried out with Gaussian modeling of the volume values, as described in previous work.²⁰ CIs were computed for sensitivity figures.

It should be noted that the sensitivity figures thus ob-

tained cannot be compared directly with the accuracy rates reported in some studies. Accuracy is the ratio of all the correctly classified individuals to the total number of individuals, and as such is a weighted mean of sensitivity and specificity, in that greater weight is attributed to the most numerous group. When one of the groups is much smaller than the other (as is the case with our FTD patients and control subjects), high accuracy rates can be obtained even when most of the "minority" group patients are misclassified. Because the aim of the current analysis was to assess how far the distribution of atrophy in FTD and AD patients was from that of control subjects, a fair comparison between the FTD and the AD groups required equalization of the weights of the two groups. This was obtained by setting a fixed specificity cutoff for the control subjects.

Results. Table 1 shows that FTD patients, control subjects, and AD patients had increasingly older age. FTD patients were less frequently women than both AD patients and control subjects. A family history of dementia was more frequent, although not significant, in the FTD group. On historic examination, memory disturbances and topographic disorientation at onset were more frequent in AD patients, whereas behavioral, oral, and dietary changes and language disturbances were more frequent in FTD patients. This symptom pattern is in agreement with recent findings by Miller et al.¹³ Daily function, as reported by the informant, was (both at onset and at the time of examination) consistent with the reported memory disturbances in the vast majority of AD patients. On the contrary, most FTD patients usually had a level of daily function much better than could be expected on the basis of the memory disturbances reported by the informant. FTD patients scored lower than AD patients on MMSE and language production. However, global indicators of dementia severity were not consistent with different severity in the two patient groups. Although not reaching statistical significance, mean disease duration, the distribution of CDR scores (42% of FTD patients were stage 0.5 versus 27% of AD patients), and instrumental disability seem to indicate milder disease severity in FTD patients (instrumental disability showed a statistical trend toward significance: $p = 0.09$). The apolipoprotein E $\epsilon 4$ allele was increased only in the AD group. Lastly, EEG results were abnormal in 3 FTD patients (25%) and 9 AD patients (37%; $p =$ not significant), and primitive reflexes were present in 9 FTD patients (75%) and 14 AD patients (47%; $p =$ not significant).

The relation between hippocampal and ERC volumes with age in the control subjects was assessed with both correlation and locally weighted regression analyses (data not shown). Neither method was able to show any association of hippocampal and ERC volumes with age. The relation of volumes with gender and age was assessed with ANOVA, with hippocampal and ERC volumes as dependent variables and gender and age (< 69 years and ≥ 70 years) as factors. Main effects and interactions of gender and age never approached significance. This observation allowed us to perform the following analyses with no need to control for the effect of age and gender.

Table 2 shows that both hippocampal and ERC volumes were smaller in FTD and AD patients than control subjects. The greatest loss was present in the hippocampi of the AD group (28 to 32% volume loss relative to control

Table 1 Sociodemographic and clinical features of the study groups

Feature	Frontotemporal dementia patients (n = 12)		AD patients (n = 30)		Control subjects (n = 30)		<i>p</i> Value*
	Mean ± SD or n (%)	Range	Mean ± SD or n (%)	Range	Mean ± SD or n (%)	Range	
Sociodemographics							
Age, y	63 ± 5	54–71	73 ± 9	53–86	69 ± 9	53–86	0.002
Women	3 (25)	—	23 (77)	—	20 (67)	—	0.006
Education, y	7 ± 4	3–17	7 ± 4	2–18	8 ± 3	5–19	NS
Dementia features on history							
Family history of dementia	7 (58)	—	9 (30)	—	—	—	NS
Memory disturbances	4 (33)	—	25 (83)	—	—	—	0.005
Behavioral disturbances or changes of oral/dietary behavior	11 (92)	—	6 (20)	—	—	—	<0.0005
Language disturbances	7 (58)	—	1 (3)	—	—	—	<0.0005
Topographic disorientation	0 (0)	—	22 (73)	—	—	—	<0.0005
Consistency between reported memory and daily function	1 (8)	—	26 (87)	—	—	—	<0.0005
Cognition							
Mini-Mental State Examination score	15 ± 8	0–29	20 ± 4	12–27	29 ± 1	25–30	<0.0001
Controlled Oral Word Association Test score	4 ± 6	0–16	15 ± 8	0–29	27 ± 10 [†]	10–56	<0.0001
Dementia severity							
Disease duration, mo	30 ± 14	12–60	41 ± 25	9–120	—	—	NS
Clinical Dementia Rating							
0.5	5 (42)	—	8 (27)	—	—	—	—
1	3 (25)	—	14 (47)	—	—	—	—
2–3	4 (33)	—	8 (27)	—	—	—	—
Basic ADL (one or more functions lost)	5 (42)	0–3	11 (37)	0–4	—	—	NS
Instrumental ADL (five or more functions lost)	1 (8)	0–8	10 (33)	0–8	—	—	NS
Apolipoprotein E ε4 carriers‡	2/11 (27)	—	14/28 (50)	—	6/28 (21)	—	0.05

* Significance on one-way analysis of variance, *t*-test, or chi-square test.

[†] Data from 66 historic control subjects.

[‡] Genotype was missing for one frontotemporal dementia patient, two AD patients, and two control subjects.

NS = not significant; ADL = activities of daily living.

subjects), whereas the least loss was in the hippocampi of the FTD group (16 to 21%). Thus, there was a significant trend toward decreasing hippocampal volumes from control subjects through FTD to AD patients, with the FTD patients having hippocampal volumes intermediate between control subjects and AD patients. This was not true for the ERC, the volumes of which were similarly atrophied in both FTD and AD patients. Table 2 also shows that although the left hippocampus was smaller than the right hippocampus in the control subjects, this was not true in either patient group. The ERC volumes were symmetric in all groups.

The distribution of hippocampal and ERC volumes by levels of dementia severity is shown in table 3. Hippocampal atrophy tended to be greater in the more severe cases both in FTD and AD patients, as indicated by the statistical significance of the severity main effect on ANOVA. The significance of the diagnosis main effect confirmed what was suggested by the data reported in table 2—hippocam-

pal atrophy was greater in AD patients than in FTD patients. The lack of significance of the interaction terms indicates that the effect of diagnosis on atrophy was present and of similar magnitude in both severity levels.

ERC atrophy was distributed differently from hippocampal atrophy. Greater ERC atrophy was again present in the more severe cases (the severity main effect was significant), but ERC atrophy was similar in FTD and AD patients (the diagnosis main effect was not significant). Once again, the interaction terms were not significant, indicating that these effects were not modified by each other.

The last step of the analysis addressed the issue of precocity of detectable atrophic changes in FTD and AD. The underlying assumption is that, on a cross-sectional basis, the brain structure in which atrophy first develops is also the structure with the volumetric measures that are furthest from normal, and as a consequence is also the one most efficient in the discrimination of those patients from

Table 2 Volumes of the hippocampus and entorhinal cortex

Area	Frontotemporal dementia patients (n = 12)			AD patients (n = 30)			Control subjects (n = 30)		p Value for trend¶
	Mean ± SD	Range	Loss* (%)	Mean ± SD	Range	Loss* (%)	Mean ± SD	Range	
Hippocampus	L = R†			L = R†			L < R‡		
Left	11.6 ± 3.2	4.7–16.2	-16	10.0 ± 2.6	3.9–14.8	-28	13.8 ± 2.4	8.9–18.3	0.04
Right	11.9 ± 3.4	4.5–19.3	-21	10.2 ± 2.8	4.8–15.1	-32	15.0 ± 2.4	9.2–20.9	0.006
Smallest§	11.0 ± 3.0	4.5–16.2	-19	9.3 ± 2.6	3.9–14.7	-32	13.6 ± 2.2	8.9–18.3	0.02
Entorhinal cortex	L = R†			L = R†			L = R†		
Left	5.6 ± 2.2	2.3–8.8	-28	5.9 ± 1.8	2.9–9.0	-28	8.1 ± 2.0	4.6–13.3	NS
Right	6.4 ± 2.6	2.6–10.8	-27	6.3 ± 2.1	2.8–11.4	-27	8.6 ± 2.2	5.2–14.3	NS
Smallest§	5.2 ± 1.9	2.3–8.0	-28	5.5 ± 1.6	2.8–8.5	-28	7.6 ± 1.8	4.6–12.7	NS

All mean volumes of patients are significantly different from control subjects at $p < 0.05$.

* Percent loss with respect to the mean value of control subjects.

† L = R, volumes not significantly different between sides.

‡ L < R, left volume significantly ($p < 0.05$) smaller than the right on *t*-test for paired samples.

§ The most atrophic between the right and the left sides for each individual subject.

¶ Significance of decreasing mean volumes from control subjects, through frontotemporal dementia, to AD patients (adjusted for age, gender, and dementia severity).

NS = not significant.

normal control subjects. Table 4 shows the results of discriminant analysis and Gaussian modeling of volume values. Of the right, left, and smallest hippocampi, the right was the best in discriminating both FTD and AD patients from control subjects, whereas for the ERC the most atrophic between the right and the left side was the best discriminator. The accuracy of the classification based on the discriminant analysis algorithm was variable, but consistently lower for the ERC for both patient groups. When specificity was set at 90%, the sensitivity for the detection of FTD patients from control subjects was approximately 50% for both hippocampal and ERC volumes. Under the same circumstances, the hippocampus performed better

than the ERC only in the detection of AD patients, with sensitivity reaching 80%.

Discussion. We have shown that 1) the hippocampus and the ERC are atrophic in FTD, 2) atrophy of the hippocampus in FTD is less severe than in AD but the atrophy of the ERC is equally severe, 3) hippocampal and ERC atrophy follow the clinical progression of dementia severity in both patient groups, and 4) neither hippocampal nor ERC atrophy was particularly sensitive in discriminating FTD patients from control subjects, whereas the hippocam-

Table 3 Hippocampal and entorhinal cortex volumes by dementia severity

Area	Frontotemporal dementia				AD				ANOVA*		
	CDR 0.5/1 (n = 8)		CDR 2/3 (n = 4)		CDR 0.5/1 (n = 22)		CDR 2/3 (n = 8)		Main effects		Interaction†, diagnosis × severity
	Mean ± SD	Loss (%)	Mean ± SD	Loss (%)	Mean ± SD	Loss (%)	Mean ± SD	Loss (%)	Diagnosis	Severity	
Hippocampus											
Left	12.6 ± 1.7	-9	9.8 ± 4.9	-29	10.5 ± 2.5	-24	8.5 ± 2.2	-38	0.05	0.01	NS
Right	13.3 ± 2.5	-11	9.2 ± 3.4	-39	10.6 ± 2.7	-29	8.9 ± 2.7	-41	0.04	0.02	NS
Smallest‡	12.3 ± 1.8	-10	8.4 ± 3.5	-38	9.9 ± 2.6	-27	7.8 ± 2.1	-43	0.03	0.003	NS
Entorhinal cortex											
Left	6.4 ± 1.3	-21	4.2 ± 3.1	-48	6.5 ± 1.6	-20	4.2 ± 0.9	-48	NS	0.009	NS
Right	6.8 ± 2.5	-21	5.4 ± 2.8	-37	6.9 ± 2.1	-20	4.6 ± 1.0	-47	NS	0.0005	NS
Smallest‡	5.8 ± 1.3	-24	3.9 ± 2.5	-49	6.0 ± 1.6	-21	4.1 ± 1.9	-46	NS	0.001	NS

* Values denote significance in models with main effects only and (†) full factorial models.

‡ The most atrophic between the right and the left sides for each individual subject.

CDR = Clinical Dementia Rating; ANOVA = analysis of variance.

Table 4 Sensitivity to separate frontotemporal dementia (FTD) and AD patients from 30 control subjects by atrophic changes of the hippocampus and entorhinal cortex

Area	FTD (n = 12)	AD (n = 30)
Hippocampus		
Predictor*	Right side	Right side
Accuracy‡	11/21 (92/70%)	24/27 (80/90%)
Sensitivity§	49%, 21 to 77%	80%, 66 to 94%
Entorhinal cortex		
Predictor*	Smallest†	Smallest†
Accuracy‡	8/21 (67/70%)	20/20 (67/67%)
Sensitivity§	52%, 24 to 80%	45%, 28 to 62%

* Variable selected by the discriminant algorithm as the best discriminator.

† The most atrophic between the right and the left side for each individual subject.

‡ Number (percentage) of subjects (FTD/control subjects and AD/control subjects) classified correctly by discriminant analysis. Percentages denote sensitivity/specificity figures.

§ Percentage of FTD and AD patients, and 95% CI classified correctly on the basis of the volume values with specificity set at 90%.

pal volumes could differentiate AD patients from control subjects with remarkable sensitivity. The data lead us to hypothesize that detectable *in vivo* atrophy of the hippocampus is not an early event in FTD, or as severe in nature, and confirms that this is the case in AD.

These data are consistent with the view that it is possible to identify patterns of atrophy that characterize the primary degenerative dementias. We have shown previously⁴ that FTD patients can be differentiated simultaneously from AD patients and control subjects with 79% sensitivity and 83% specificity on the basis of measures of atrophy in different brain areas. Enlargement of the temporal horn (mainly the left), frontal atrophy, and sparing of the parahippocampal region were characteristic of FTD, whereas milder frontal atrophy and more severe parahippocampal atrophy was characteristic of AD. The current study indicates that this pattern might be enriched by the findings of milder hippocampal atrophy in FTD and equally severe ERC atrophy.

One relevant question arising from these results is whether the patterns of atrophy are specific for a given pathologic entity or whether they are specific for a syndrome. FTD and AD are pathologically distinct. FTD consists of nonspecific neuronal loss and gliosis affecting more severely the anterior regions (frontal and temporal) of the brain, whereas AD is characteristically a plaque-and-tangle disease of the medial temporal lobe and limbic areas. In general, in FTD, behavioral and language disturbances are particularly striking features early in the course of the disease, whereas learning abilities are relatively spared; the opposite is true of AD. The relatively more severe frontal atrophy and enlargement of the left temporal horn, and the milder hippocampal atro-

phy in FTD patients might at least partly account for these clinical features. However, AD may have an atypical presentation with prominent behavioral and language disturbances, and sparing of memory also in its early phases.³⁴ It is currently unknown whether the atrophic pattern of atypical cases of AD resembles more closely FTD or typical AD. Therefore, how much of the observed atrophic pattern is due to underlying different pathology or to different affected brain regions remains to be investigated further. It should also be recognized that the presence of some patients with AD pathology in our FTD group might have a significant effect on the current results.

One of the unique findings of this study regards atrophy of the ERC. Although early attempts to quantify ERC atrophy with MRI date back to at least 1991,² detailed guidelines of MR anatomy of the ERC have been only recently introduced.³³ Based on these guidelines, Jouttonen et al.³⁵ have shown that the ERC is atrophic in AD patients of mild to moderate severity when compared with control subjects. These findings are confirmed in our own AD patients. However, at least two questions have arisen from our data on ERC atrophy.

First, the ERC is believed to be affected by AD pathology in the very early stages of the disease, even before changes in the hippocampus can be appreciated.¹⁹ Our AD data suggest that, *in vivo*, the atrophic changes that can be appreciated most easily are those of the hippocampus rather than those of the ERC. Compared with the hippocampus, this may be due to limitations of MRI to measure accurately the complicated anatomy of smaller structures, such as the ERC, particularly due to occasionally poor gray-white matter contrast within the parahippocampal gyrus. It may, however, also reflect the true pattern of volumetric pathology. It is noteworthy that, although pathologic hallmarks of AD such as neurofibrillary tangles may first appear in the ERC,¹⁹ the presence of these changes does not equal volumetric atrophy *per se*. This view is supported by evidence from studies of demented patients and cognitively normal elders. In autopsied brains of AD patients, Mizutani and Kasahara³⁶ have shown that at least part of the macroscopic hippocampal atrophy of AD can be secondary to microscopic changes of the ERC. Furthermore, although plaques and tangles were present in biopsy material taken from the hippocampi of cognitively intact older individuals,³⁷ some volumetric MRI studies have not found any significant correlation with hippocampal^{38,39} or ERC³³ volumes with age. These observations suggest that microscopic changes that are believed to be pathologic are not mirrored invariably by macroscopic changes.

Second, the reason why the ERC should be atrophic in FTD needs explanation, because the primary site of the pathology is believed to lie elsewhere (i.e., in the anterior frontal and temporal cortices). The ERC was involved heavily in the pathologic process

in some sporadic and familial cases of FTD.²¹⁻²³ Sima et al.²³ have speculated that in the chromosome 17-associated form of FTD the involvement of the ERC might be interpreted in the light of the more widespread involvement of corticobasal ganglionic circuits encompassing the entorhinal, anterior temporal, and cingulate projections to the ventral striatum, as well as of the projections from the pyriform cortex and amygdala to the ERC. Alternatively, it can be hypothesized that ERC atrophy simply might be a deafferentation phenomenon following frontal and temporal damage. In fact, it has been shown in the monkey that the major afferents to the ERC come from the ventral frontal and temporal cortex.⁴⁰

The hippocampal atrophy of our FTD patients also deserves some discussion. Pathologic descriptions of the hippocampal region are discordant regarding the presence and severity of hippocampal atrophy in FTD, but some observations indicate that hippocampal involvement can occur. Knopman et al.⁸ have reported hippocampal atrophy in dementia lacking distinctive histology, a condition linked closely to FTD. Although this finding has not been confirmed,⁹ Mann et al.¹⁴ and Mann and South¹⁵ also reported hippocampal atrophy in FTD. An independent confirmation of our findings of greater hippocampal atrophy in FTD patients than control subjects has been reported recently.⁴¹ Furthermore, Mann et al.¹⁴ pointed out that the hippocampus was not involved in their cases of FTD associated with motor neuron disease. None of our FTD patients had motor neuron disease at the time of evaluation, although one developed motor neuron involvement approximately 2 years after onset of the cognitive and behavioral changes, but his atrophic pattern was similar to that of the other FTD patients. Lastly, it should be stressed that the pattern of milder involvement of the hippocampus with more severe involvement of the ERC is similar to that reported on pathologic examination of the brains of patients affected by chromosome 17-associated FTD.²³

Recent studies have shown hippocampal or medial temporal lobe atrophy also in other primary degenerative brain diseases such as PD with no dementia,^{3,5} PD with dementia,³ and Lewy body dementia,⁵ in addition to the well-known atrophic changes of the hippocampus in AD.^{1,2,18,38} Our data of decreased hippocampal volume in FTD indicate that this might be one more degenerative brain disease showing hippocampal involvement. This anatomic finding should be interpreted in the light of the clinical features of the disease. It has been argued that hippocampal and medial temporal lobe atrophy might be the biological substrate for the memory disturbance that is often present in some non-AD primary degenerative brain diseases.^{3,5} We have already pointed out that the characteristic sparing of learning and memory in FTD might be partly explained by the relatively less severe, compared with AD, hippocampal atrophy that we found in our FTD patients. However, the preservation of some brain areas involved in the

memory processes, such as the parahippocampal region,⁴ might also be contributing factors. The contributing role of parahippocampal atrophy to memory deficits is supported by human and animal data. In fact, relevant atrophic changes of the parahippocampal region have been demonstrated in vivo in AD patients with memory disturbances⁴² of even a mild severity.²⁰ In the monkey, it has been shown that bilateral lesions of the ERC, which spare the parahippocampal cortices, produce only minor and reversible impairment on a task of visual recognition memory.⁴³ In contrast, animals with bilateral lesions of the parahippocampal cortices, which spare the ERC and the hippocampal formation, produce a robust and enduring memory deficit on this task.⁴⁴

Some limitations of this study should be noted. Age, gender, and disease severity were different in our FTD and AD patients. However, although some investigators have found greater hippocampal atrophy with advancing age in normal elders,¹⁸ neither hippocampal nor ERC volumes were associated with age in the group of normal control subjects of our own and other series.^{33,38,39,45} Moreover, hippocampal and ERC volumes have been shown in our own and other series³⁸ of normal elders to be similar in men and women, once adjusted for head size. For these reasons, different age and gender in patient groups should not have contributed to the results of the study.

The matching of dementia severity between FTD and AD patients is a more uncertain issue. In fact, although the MMSE score was clearly indicative of greater severity in the FTD group, other disease severity indicators (disease duration, CDR, and basic and instrumental disability) pointed toward either no difference or a slightly greater severity in the AD group. Because the MMSE is based mainly on verbal tasks, it may not be well suited to measure global dementia severity in conditions such as FTD, in which language disturbances are particularly severe. Indeed, our FTD patients had language disturbance more severe than that of our AD patients, as shown by a test specifically aimed to assess language production (verbal fluency test). It should also be noted that even if global dementia severity were greater in FTD patients, this would enhance rather than decrease the magnitude and significance of most findings of this study (lower hippocampal atrophy in FTD, and poor discrimination of FTD patients from control subjects by hippocampal and ERC measures). It could be argued that disease duration is a better indicator of dementia severity in conditions in which cognitive or functional instruments are not applicable. Indeed, although not significant, disease duration was almost 1 year shorter in our FTD patients than in our AD patients, which might partly account for the milder hippocampal atrophy of FTD patients. Future volumetric studies of FTD patients might try and match them carefully with AD patients of equal disease duration.

Pathologic specimens were not available for any of

these patients. However, all patients were followed clinically for at least 2 years. Although this does not provide certainty of diagnosis, it should at least help to reduce the diagnostic error. Indeed, one of the 14 original FTD patients⁴ was excluded from the current study because he did not show any cognitive and functional deterioration over the following 2 years. All analyses previously published⁴ were rerun with the exclusion of this patient, but the results showed only minimal changes, confirming the stability of the findings. Moreover, we tried to reduce the pathologic heterogeneity of the FTD group by excluding those patients who might have had Pick's disease, but the accuracy of this procedure can hardly be checked. The only supportive argument is that the proportion of Pick's to non-Pick's forms in our series (4 of 14, 29%) is close to that reported in other autopsy-proved series (25%).¹¹ Indeed, this is the first study of brain volumetric analysis of FTD patients, and confirmation of these findings in other series is certainly warranted.

We believe that the results of this study are relevant because they add a piece of information to the outline of the volumetric patterns of brain atrophy of the degenerative diseases that are being defined by current research worldwide.

Acknowledgment

The authors gratefully acknowledge the help of Drs. Giovanni Puppini and Ghassan El-Dhalati, Institute of Radiology, University of Verona, in the management of the image files. Dr. Giuliano Binetti, IRCCS San Giovanni di Dio-FBF, Brescia, provided the neuropsychological data. Drs. Tiziana Metitieri and Alessandra Pezzini helped with the data collection.

References

1. Jack CR, Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* 1992;42:183-188.
2. Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. *Neurology* 1991;41:51-54.
3. Laakso MP, Partanen K, Riekkinen P Jr, et al. Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology* 1996;46:678-681.
4. Frisoni GB, Beltramello A, Geroldi C, Weiss C, Bianchetti A, Trabucchi M. Brain atrophy in frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1996;61:157-165.
5. Double KL, Halliday GM, McRitchie DA, Reid WG, Hely MA, Morris JG. Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. *Dementia* 1996;7:304-313.
6. Lavenu I, Pasquier F, Lebert F, Pruvo JP, Petit H. Explicit memory in frontotemporal dementia: the role of medial temporal atrophy. *Dementia Geriatr Cogn Disord* 1998;9:99-102.
7. Pantel J, Schroder J, Essig M, et al. Quantitative magnetic resonance imaging in geriatric depression and primary degenerative dementia. *J Affect Disord* 1997;42:69-83.
8. Knopman DS, Mastri AR, Frey WH, et al. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. *Neurology* 1990;40:251-266.
9. Giannakopoulos P, Hof PR, Bouras C. Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. *Acta Neuropathol* 1995;89:346-355.
10. Jackson M, Lennox G, Lowe J. Motor neurone disease— inclusion dementia. *Neurodegeneration* 1996;5:339-350.
11. Gustafson L. Frontal lobe degeneration of non-Alzheimer

- type. II. Clinical picture and differential diagnosis. *Arch Gerontol Geriatr* 1987;6:209-223.
12. Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1994;57:886-896.
13. Miller BL, Ikonte C, Ponton M, et al. A study of the Lund-Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. *Neurology* 1997;48:937-942.
14. Mann DMA, South PW, Snowden JS, Neary D. Dementia of frontal lobe type: neuropathology and immunohistochemistry. *J Neurol Neurosurg Psychiatry* 1993;56:605-614.
15. Mann DM, South PW. The topographic distribution of brain atrophy in frontal lobe dementia. *Acta Neuropathol* 1993;85:334-340.
16. Niizato K, Tsuchiya K, Tominaga I, Kato Y, Ikeda K. Pick's disease with amyotrophic lateral sclerosis (ALS): report of two autopsy cases and literature review. *J Neurol Sci* 1997;148:107-112.
17. Filley CM, Kleinschmidt-De Masters BK, Gross KF. Non-Alzheimer fronto-temporal degenerative dementia. A neurobehavioral and pathologic study. *Clin Neuropathol* 1994;13:109-116.
18. Kaye JA, Swihart T, Howieson D, et al. Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. *Neurology* 1997;48:1297-1304.
19. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239-259.
20. Frisoni GB, Beltramello A, Weiss C, Geroldi C, Bianchetti A, Trabucchi M. Linear measures of atrophy in mild Alzheimer's disease. *AJNR Am J Neuroradiol* 1996;17:913-923.
21. Kinoshita A, Tomimoto H, Suenaga T, Akiguchi I, Kimura J. Ubiquitin-related cytoskeletal abnormality in frontotemporal dementia: immunohistochemical and immunoelectron microscope studies. *Acta Neuropathol* 1997;94:67-72.
22. Hayashi M, Kobayashi K, Ishida C, et al. Non-Alzheimer dementia with status spongiosus and neuronal cell loss showing unusual perineuronal structures and point mutation at 129 codon of prion protein. *Dementia Geriatr Cogn Disord* 1997;8:55-59.
23. Sima AA, Defendini R, Keohane C, et al. The neuropathology of chromosome 17-linked dementia. *Ann Neurol* 1996;39:734-743.
24. Bergmann M, Kuchelmeister K, Schmid KW, Kretschmar HA, Schroder R. Different variants of frontotemporal dementia: a neuropathological and immunohistochemical study. *Acta Neuropathol* 1996;92:170-179.
25. Jackson M, Lowe J. The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol* 1996;91:127-134.
26. Frisoni GB, Pizzolato G, Geroldi C, Rossato A, Bianchetti A, Trabucchi M. Dementia of frontal type: neuropsychological and [99Tc]-HMPAO SPECT features. *J Geriatr Psychiatry Neurol* 1995;8:42-48.
27. Knopman DS, Christensen KJ, Shut LJ, et al. The spectrum of imaging and neuropsychological findings in Pick's disease. *Neurology* 1989;39:362-368.
28. McKhann G, Drachman D, Folstein MF, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group. *Neurology* 1984;34:939-944.
29. Rozzini L, Lussignoli G, Padovani A, Bianchetti A, Trabucchi M. Alzheimer disease and frontotemporal dementia. *Arch Neurol* 1997;54:350. Letter.
30. Magni E, Binetti G, Bianchetti A, Rozzini R, Trabucchi M. Mini-Mental State Examination: a normative study in an Italian elderly population. *Eur J Neurol* 1996;3:198-202.
31. Hughes CP, Berg L, Danziger WL, Coben LA, Martin LA. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566-572.
32. Frisoni GB, Padovani A, Binetti G, Magni E, Bianchetti A, Trabucchi M. GEMS (global evaluation of mental status): a multidimensional neuropsychological tool for dementia assessment. Presented at the VI Congress of the International Psychogeriatric Association; October 19, 1993; Berlin, Germany. Symposium 72.
33. Insausti R, Juottonen K, Soininen H, et al. MRI volumetric

- analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am J Neuroradiol* 1998;19:659–671.
34. Jagust WJ, Davies P, Tiller-Borchik JK, Reed BR. Focal Alzheimer's disease. *Neurology* 1990;40:14–19.
 35. Juottonen K, Laakso MP, Insausti R, et al. Volumes of the entorhinal and perirhinal cortices in Alzheimer's disease. *Neurobiol Aging* 1998;19:15–22.
 36. Mizutani T, Kasahara M. Hippocampal atrophy secondary to entorhinal cortical degeneration in Alzheimer-type dementia. *Neurosci Lett* 1997;222:119–122.
 37. Arriagada PV, Marzloff K, Hyman BT. Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. *Neurology* 1992;42:1681–1688.
 38. Laakso MP, Soininen H, Partanen K, et al. MRI of the hippocampus in Alzheimer's disease: sensitivity, specificity and analysis of the incorrectly classified subjects. *Neurobiol Aging* 1998;19:23–31.
 39. DeCarli C, Murphy DGM, Gillette JA, et al. Lack of age-related differences in temporal lobe volume of very healthy adults. *AJNR Am J Neuroradiol* 1994;15:689–696.
 40. van Hoesen GW, Pandya DN, Butters N. Cortical afferents to the entorhinal cortex of the rhesus monkey. *Science* 1972;175:1471–1473.
 41. Hartikainen P, Laakso MP, Lehtovirta M, Riekkinen P Jr, Partanen K, Soininen H. Volumes of hippocampus in the clinical and MRI-based diagnosis of frontotemporal dementia with a reference to Alzheimer's disease and Parkinson's disease. *Neurology* 1998;50(suppl 4):A161. Abstract.
 42. Jobst KA, Smith AD, Szatmari M, et al. Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. *Lancet* 1992;340:1179–1183.
 43. Leonard BW, Amaral DG, Squire LR, Zola-Morgan S. Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. *J Neurosci* 1995;15:5637–5659.
 44. Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J Neurosci* 1989;9:4355–4370.
 45. Bigler ED, Blatter DD, Anderson CV, et al. Hippocampal volume in normal aging and traumatic brain injury. *AJNR Am J Neuroradiol* 1997;18:11–23.

Cerebral metabolite abnormalities correlate with clinical severity of HIV-1 cognitive motor complex

L. Chang, MD; T. Ernst, PhD; M. Leonido-Yee, MD; I. Walot, MD; and E. Singer, MD

Article abstract—*Objective:* To investigate the relation between biochemical alterations and disease severity in HIV-cognitive motor complex (HIV-CMC). *Background:* HIV-CMC encompasses both the milder form (HIV-minor cognitive motor disorder [HIV-MCMD]) and the more severe form (HIV-dementia). There is no validated marker to monitor disease severity noninvasively. *Methods:* A total of 54 patients with HIV-CMC (20 with HIV-MCMD, 34 with HIV-dementia) and 29 seronegative healthy volunteers were evaluated for cerebral metabolite abnormalities using proton (¹H) MRS in the frontal cortex, frontal white matter, and basal ganglia. *Results:* The three subject groups showed different concentrations of myoinositol (MI; $p = 0.0005$) and choline-containing compounds (CHO; $p = 0.004$) in the frontal white matter. HIV-dementia patients had metabolite changes in all three brain regions whereas HIV-MCMD patients had abnormalities in the frontal white matter only. HIV-CMC patients had elevated MI ($p < 0.0001$) and CHO ($p = 0.004$) levels with increasing AIDS dementia complex stage, and *N*-acetyl compounds (NA) were decreased only in moderate to severe stages of dementia. Furthermore, CD4 count and CSF viral load, but not plasma viral load, showed significant effects on cerebral metabolite concentrations, which in turn showed significant effects on the HIV-dementia scale. *Conclusions:* In early stages of HIV-CMC, frontal white matter showed evidence of glial proliferation (with elevated MI and CHO levels) and cell membrane injury (with increased CHO levels), but no significant neuronal injury (with normal NA concentrations). HIV-MCMD and HIV-dementia patients have different neurochemical abnormalities. Because these biochemical alterations are related to clinical disease severity, they may be useful surrogate markers for noninvasive quantitative assessment of brain injury in patients with HIV-CMC.

NEUROLOGY 1999;52:100–108

CNS involvement is common in patients infected with HIV-1. In the early stages of HIV-1 infection, the virus can invade the brain directly, causing a subclinical encephalitis.^{1,2} As the disease progresses,

the virus undergoes a long incubation period before rendering its host immunocompromised and susceptible to other opportunistic infections. At the later stage of AIDS, approximately 20% of these patients

From the Departments of Neurology (Drs. Chang, Ernst, Leonido-Yee, and Singer) and Radiology (Drs. Ernst and Walot), University of California Los Angeles School of Medicine, Harbor-UCLA Medical Center, Torrance, CA.

Supported by grants from the National Institutes of Health, Scientist Development Award for Clinicians (L.C.; DA00280) and grant GCRC M01-RR00425.

Received February 19, 1998. Accepted in final form September 1, 1998.

Address correspondence and reprint requests to Dr. Linda Chang, Department of Neurology, 1000 W. Carson Street, B-4, Harbor-UCLA Medical Center, Torrance, CA 90509.