Brain atrophy in frontotemporal dementia

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Abstract

Objective—To evaluate the pattern of regional brain atrophy in patients with frontotemporal dementia by comparing it with that in patients with Alzheimer's disease and normal controls.

Methods—Fourteen patients with frontotemporal dementia, 13 with moderate, and 33 with mild Alzheimer's disease, and 31 controls were studied. Atrophy was evaluated with linear measures in the anterior brain, medial temporal lobe, and hippocampal formation regions using MRI.

Results—Patients with frontotemporal dementia had greater atrophy in the anterior brain regions than patients with Alzheimer's disease or controls. Atrophy of the hippocampal formation, which best discriminates Alzheimer's disease from controls, was present also in patients with frontotemporal dementia. By contrast, atrophy of the medial temporal lobe, which is also present in Alzheimer's disease, was absent in frontotemporal dementia.

Conclusion—A pattern of atrophy in the frontal lobes and hippocampal formation with sparing of the medial temporal lobe might be distinctive of frontotemporal dementia. Hippocampal involvement might not be specific for Alzheimer's disease and specific patterns of atrophy might be distinctive of some forms of degenerative dementia.

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Frontotemporal dementia is the most prevalent of non-Alzheimer's degenerative dementias.¹⁻³ Its main clinical features are relative sparing of learning, pre-eminent behavioural and language disturbances, frontotemporal hypoperfusion on single photon emission computed tomography (SPECT), and progressive course.¹⁻⁶ The most relevant neuropathological findings are vacuolar degeneration, gliosis, neuronal loss, and atrophy in the anterior regions of the frontal and temporal lobes.² Guidelines for in vivo diagnosis of frontotemporal dementia have recently been issued.⁷

Atrophy in the medial temporal lobe region (hippocampal formation, parahippocampal gyrus, and amygdala) as detected with MRI

has been consistently found in Alzheimer's disease,⁸⁻¹⁵ even in its early stages,⁸ and increasing atrophy over time has been found in subjects at risk.¹⁶ Measurements focusing on the hippocampus yield the highest sensitivity,^{8 10 14} and these have been proposed as a marker of Alzheimer's disease.¹⁷ However, the specificity of hippocampal atrophy for Alzheimer's disease is doubtful, as it has been reported in at least two other conditions: temporal lobe epilepsy and schizophrenia.^{18 19} Although a radiological marker able to differentiate these conditions from Alzheimer's disease is of little practical interest, it is much more relevant in the differential diagnosis of frontotemporal dementia. However, in vivo data on brain atrophy in frontotemporal dementia are not available.

The aims of the study were to investigate the pattern of brain atrophy of frontotemporal dementia and to assess the usefulness of measures of atrophy in the discrimination of frontotemporal dementia from Alzheimer's disease and controls.

Materials and methods

SUBJECTS

This study comprised 14 patients with frontotemporal dementia, 46 with Alzheimer's disease (33 of mild and 13 of moderate severity), and 31 normal controls. All patients and controls were consecutively recruited at the Alzheimer's Disease Unit, Brescia, Italy, from 1 September 1993 to 15 December 1994.

Diagnosis of frontotemporal dementia was made on clinical grounds following clinico-pathological descriptions^{3 6} and recently issued guidelines.⁷ All patients with frontotemporal dementia underwent brain SPECT with HMPAO, invariably showing anterior hypoperfusion.^{5 20} It should be underlined that SPECT was not used as an inclusion criterion, as all patients suspected of frontotemporal dementia on clinical grounds did show anterior hypoperfusion.²⁰ As a further confirmation, all SPECT images of frontotemporal dementia and 14 images of patients with Alzheimer's disease of similar severity were sorted blind to diagnosis by one of us (AB) into those who showed a frontal hypoperfusion pattern and those who did not. All patients with frontotemporal dementia were included in the group showing frontal hypoperfusion. Two patients with very severe atrophy on MRI and mild to moderate cognitive deterioration suggesting Pick's disease²¹ and two with progressive aphasia in the absence of other cognitive and behavioural

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disturbances²² were not included in the study. Mini mental state examination (MMSE)²³ of patients with frontotemporal dementia ranged between 0 and 29. All patients were followed up from a minimum of eight months to a maximum of two years, and diagnosis of frontotemporal dementia was always confirmed at follow up. All patients had deteriorated mainly on language and behaviour.

Patients with Alzheimer's disease met NINCDS-ADRDA criteria for probable disease.²⁴ Patients meeting these criteria but with clinical features suggesting dementia of the Lewy body type²⁵ were not included in the study. Patients with mild and moderate Alzheimer's disease had MMSEs of > 20 and between 12 and 19 respectively.

All patients were staged according to a scale grading overall severity of dementia (clinical dementia rating),²⁶ which compounds information on memory disturbances and daily function. A complete history with basic and instrumental activities of daily living (BADL and IADL) assessment^{27,28} was taken from a proxy informant. Laboratory studies included complete blood count, chemistry profile, chest radiograph, thyroid function, B12, folic acid, ECG, EEG, and CT. Neurological examination was performed by a neurologist, and physical examination of all systems by a geriatrician. Neuropsychological testing²⁹ was performed by a psychologist and included MMSE and tests tapping constructional apraxia (copy of Rey-Osterreith figure),³⁰ and verbal (logical memory test, verbal learning subscale of the global evaluation of mental status)^{31,32} and non-verbal (recall of Rey-Osterreith and Wechsler memory scale figures)^{30,33} learning. The global evaluation of mental status is a neuropsychological battery with a verbal learning subscale that has shown good reliability (Cronbach $\alpha = 0.80$) and known group validity in 117 moderately and 22 mildly demented patients, and 84 controls.³²

Controls were 31 patients' relatives (mostly spouses) without detectable cognitive deficit. They had a negative history of neurological disease, although some reported mild subjective memory problems which did not result in

impairment in daily activities. All had MMSE, and were judged not demented by a neurologist and a psychologist involved in the evaluation of the patients.

Apolipoprotein E phenotyping was performed on patients and controls with isoelectric focusing on plasma samples freed from lipid.³⁴

Written informed consent was obtained from patients and controls or primary carers, after discussion of the risks and benefits of participation. No compensation was provided.

MAGNETIC RESONANCE IMAGING TECHNIQUE AND ANALYSIS

Imaging was performed at the Radiology Department, University of Verona, with a 1.5 Tesla unit (Siemens, Magnetom) and a standard head coil. A 3D technique was employed for image acquisition (TR 10 s; TE 4 ms; TI 300 ms; flip angle 10°; field of view 250 mm; acquisition 2; matrix 160 × 256), allowing reconstruction of 1.3 mm thick contiguous slices. Total acquisition time was 7.40 minutes. All linear measurements were performed on T1 weighted images by the same neuroradiologist on magnified images (magnification factor 1.5 to 1.7) with the built in distance measurement software, blind to the diagnosis, age, and sex of the subject.

The following planes were identified¹⁴:

(1) The bicommissural plane on the midsagittal slice, joining the anterior with the posterior commissure. The anterior commissure is a precise anatomical landmark, and the posterior commissure was set at the level of the cranial extremity of the superior colliculi (fig 1A).

(2) The brainstem axis plane, on the midsagittal slice, parallel to the dorsal surface of the brainstem (fig 1A).

(3) The temporal lobe plane on the parasagittal slice, where the temporal lobe was best appreciated in its full length, about 20° caudal to the orbitomeatal line (fig 1B).

The following linear measurements were taken, on both sides when appropriate:

(1) Bifrontal index, measured on a plane parallel to the temporal lobe plane at the level

Figure 1 Sagittal 3D gradient echo images of a patient with Alzheimer's disease. (A) Midsagittal image showing the bicommissural plane and the brainstem axis plane. (B) Parasagittal image showing the temporal lobe plane.

Figure 2 Axial and coronal 3D gradient echo images of a patient with Alzheimer's disease. The arrows show: (A) width between the frontal horns of the lateral ventricles (inner arrows) and cranial width (outer arrows) (bifrontal index); (B): interuncal distance; (C): minimum thickness of the medial temporal lobe; (D): hippocampal height (1), width of the choroid fissure (2), and width of the temporal horn (3).

of the maximal width between the frontal horns of the lateral ventricles,³⁵ and defined as the ratio of this measure to brain width (the distance between the inner tables of the calvarium at the same level) $\times 100$ (fig 2A).³⁵

(2) Interhemispheric fissure width, measured on the same plane as the bifrontal index, and defined as the largest distance between the mesial aspects of the cerebral cortex in the interhemispheric fissure.

(3) Interuncal distance, measured on a plane parallel to the bicommissural plane at the level of the suprasellar cistern, as the distance between the uncus of the temporal lobes (fig 2B).³⁶

(4) Minimum thickness of the medial temporal lobe, measured on the temporal lobe plane, as the thickness of the medial temporal lobe considered at its narrowest point (fig 2C).⁹

(5) Hippocampal height, measured on a plane parallel to the brainstem axis plane where the hippocampal formation was highest, as the greatest height of the hippocampal formation (fig 2D).¹⁰ Cerebral width (the maximum distance between the inner tables of the calvarium) at this level was also measured.

(6) Width of the choroid fissure, measured on the same plane used for hippocampal height measurement, as the vertical width of

the choroid fissure centred on the midpoint of the hippocampal formation (fig 2D).¹⁰ This point usually lies on the line where hippocampal height is taken.

(7) Width of the temporal horn, measured on the same plane used for hippocampal height measurement (fig 2D).¹⁰ Figure 3 shows hippocampal height, width of the choroid fissure, and width of the temporal horn.

Test-retest reliability of all measures was assessed in randomly selected patients ($n = 10$) and controls ($n = 10$) with measurements on two separate occasions two to six weeks apart and blind to previous results. Intraclass

Figure 3 Schematic drawing of the hippocampal formation. (a) width of the temporal horn; (b) hippocampal height; (c) width of the choroid fissure. (Adapted from Scheltens et al.¹⁰)

Figure 4 Example of the calculation of age standardised measures. Minimum thickness of the medial temporal lobe is used as an example. MT = minimum thickness of the medial temporal lobe (mm). Open circle = patient; full circles = controls. The patient is 72 years old, and his MT is 6.9 mm. The expected normal value of MT in a 72 year old control is 13.6 mm. The value of the age standardised measure is $6.9/13.6 = 0.51$. Direct measures of atrophy, such as MT and hippocampal height indicate greater atrophy than controls for age standardised values lower than 1, and indirect measures, such as bifrontal index, interhemispheric fissure width, interuncal distance, width of the choroid fissure, and width of the temporal horn indicate greater atrophy than controls for age standardised values greater than 1.

correlation coefficients³⁷ ranged from 0.91 to 0.98 for all measures, indicating good reliability.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS.³⁸ Differences of continuous or dichotomous variables between groups were assessed with Student's *t* test or χ^2 test when appropriate. The relations of measures of brain atrophy with age and cerebral width were assessed with Pearson's *r*. Significance was set at $P < 0.05$, but values < 0.10 are reported in the tables for frontotemporal dementia and moderate Alzheimer's disease groups because of their low numbers.

The normal effect of age (and cerebral width when appropriate) on brain measures was taken into account by transforming measures into age standardised values, defined as the ratio of the observed measure to the expected value (fig 4).⁹ The expected value was computed by regressing brain measures on age and, when appropriate, cerebral width in the controls. The effect of sex on the relation between atrophy and age in the controls

was considered by general factorial analysis of variance (ANOVA). General factorial ANOVA models were built with sex, age, and their interaction as factors.

Measures of atrophy independently contributing to the prediction of disease (frontotemporal dementia, Alzheimer's disease, or control) were identified with multivariable discriminant analysis with stepwise selection of variables.³⁸ This technique minimises the overlapping between the three groups by computing two orthogonal (uncorrelated) multivariable functions allowing two scores (discriminant scores) to be computed for each subject. The discriminant scores are such that their combination in a bidimensional space results in separating the three groups with the smallest possible overlapping, resulting in maximal overall sensitivity and specificity. Measures of atrophy contributing to the separation of the groups were assessed in discriminant models with two approaches: (a) the algorithmic approach, with stepwise selection of variables, that takes into account the independent contribution of each variable, and whichever variable was unable to increase separation of the groups was excluded from the final model. Variables were entered as age standardised values. Entering of variables was based on the smallest Wilks' λ of the discriminant function and on *F* to enter for Wilks' λ greater than 3.84. Removal of variables was based on *F* to remove values for Wilks' λ lower than 2.71; (b) a hypothesis driven approach, with a priori selection of variables. Those measures of hippocampal atrophy expected to be the best discriminators were simultaneously entered in the model.

Results

Table 1 shows clinical and demographic features of patients with frontotemporal dementia and Alzheimer's disease and controls. Patients with frontotemporal dementia were mainly men and they were younger than the other study groups both at the time of study and at onset of disease, and a trend for shorter duration of disease than in patients with moderate Alzheimer's disease was present. The prevalence of the $\epsilon 4$ allele of apolipoprotein E was similar to that found in controls, and lower than that of patients with Alzheimer's disease. The MMSE for patients with frontotemporal dementia was similar to that of patients with

Table 1 Clinical and demographic features of patients with frontotemporal dementia (FDT), Alzheimer's disease (AD), and controls

	FTD (n = 14)	Mild AD (n = 33)	Moderate AD (n = 13)	Controls (n = 31)	<i>P</i> *	<i>P</i> †	<i>P</i> ‡
Sex (men/total)	10/14 (0.71)	9/33 (0.27)	2/13 (0.15)	10/31 (0.32)	0.004	0.01	0.03
Age (y)	62.9 (5.6)	74.9 (8.0)	69.7 (9.8)	69.1 (8.6)	< 0.0005	0.04	0.02
Education (y)	7.5 (4.2)	7.5 (4.4)	6.8 (3.5)	8.2 (3.3)	NS	NS	NS
Age at onset (y)	60.4 (5.9)	71.4 (8.1)	65.7 (8.4)	—	< 0.0005	0.07	—
Disease duration (months)	30.8 (13.9)	42.0 (27.8)	47.7 (29.3)	—	NS	0.06	—
Apolipoprotein E $\epsilon 4$ allele ($\epsilon 4$ /total)§	4/24 (0.17)	26/62 (0.40)	14/26 (0.54)	8/56 (0.14)	0.05	0.01	NS
Mini mental state examination	14.6 (9.2)	22.0 (2.1)	14.5 (1.7)	29.0 (1.8)	< 0.0005	NS	< 0.0005
Instrumental activities of daily living (functions lost)	2.9 (2.7)	3.6 (2.1)	5.2 (2.8)	0.0 (0.0)	NS	0.03	< 0.0005
Clinical dementia rating	1.21 (1.01)	0.95 (0.45)	1.96 (0.66)	0.00 (0.00)	NS	0.03	< 0.0005

Values are number (proportion) for sex and apolipoprotein E $\epsilon 4$ allele, and means (SD) for all other variables.

§Apolipoprotein E phenotyping was performed in 12 patients with FTD, 31 with mild AD, all patients with moderate AD, and 28 controls. The total number of $\epsilon 4$ alleles in each group is twice the number of subjects of the group.

P = Significance on χ^2 or *t* test between FTD and: *mild AD, †moderate AD, and ‡controls. Significance values below 0.10 are reported.

Table 2 Neuropsychological features of patients with frontotemporal dementia (FTD) and Alzheimer's disease (AD)

	FTD (n = 9)	Mild AD (n = 32)	Moderate AD (n = 12)	P*	P†
Mini mental state examination	18.1 (7.3)	22.1 (2.1)	14.6 (1.7)	0.009	NS
Clinical dementia rating	0.67 (0.61)	0.95 (0.45)	1.96 (0.69)	NS	< 0.0005
Logical memory	5.7 (4.8)	4.1 (3.9)	1.6 (2.7)	NS	0.02
GEMS verbal learning	10.6 (5.7)	8.1 (3.9)	5.2 (4.4)	NS	0.02
Rey's figure copy	13.8 (12.6)	19.6 (11.7)	0.1 (0.2)	NS	0.005
Rey's figure recall	4.0 (6.3)	1.0 (1.9)	0.0 (0.0)	0.02	0.05
WMS delayed recall	1.22 (2.90)	0.10 (0.30)	0.00 (0.00)	0.04	NS

Values are means (SD).

P = Significance on *t* test between FTD and: *mild AD, and †moderate AD. Significance values below 0.10 are reported. GEMS = global evaluation of mental status battery.³² WMS = Wechsler memory scale.³³

moderate Alzheimer's disease, and lower than that of patients with mild Alzheimer's disease. However, disability in daily function and overall severity of dementia were similar to those of patients with mild Alzheimer's disease, and lower than those of patients with moderate Alzheimer's disease.

Complete neuropsychological testing was available for nine patients with frontotemporal dementia, 32 with mild, and 12 with moderate Alzheimer's disease. Those five patients with frontotemporal dementia who had not undergone complete neuropsychological testing were more impaired (mean MMSE = 8.2, ranging from 0 to 19) than those who had (MMSE = 18.1, range 10 to 29). The patients with mild and moderate Alzheimer's disease who had not undergone complete neuropsychological testing had MMSEs of 20 and 13, respectively. Table 2 shows neuropsychological features of the patient groups. Global cognitive severity in patients with frontotemporal dementia as measured with the MMSE was intermediate between that of patients with moderate and mild Alzheimer's disease. On the other hand, clinical dementia rating indicated milder impairment in frontotemporal dementia than patients with Alzheimer's disease, which was significant for patients with moderate Alzheimer's disease. Neuropsychological tests of learning were relatively spared in patients with frontotemporal dementia compared with patients with Alzheimer's disease. Verbal learning was better than patients with both mild and moderate Alzheimer's dis-

ease, but significantly so only compared with those with moderate Alzheimer's disease. Sparing of learning in frontotemporal dementia was even more pronounced for non-verbal learning. The significance for the difference of the delayed recall of the Wechsler memory scale between patients with frontotemporal dementia and those with moderate Alzheimer's disease was not reached, possibly because of few patient numbers.

Table 3 shows the rough values of all cerebral measures. All measures indicated greater atrophy in patients with Alzheimer's disease than controls, and this was true in patients with frontotemporal dementia except for minimum thickness of the medial temporal lobe, which had values similar to controls. Width of the temporal horn, a measure shown to be a sensitive discriminator between Alzheimer's disease and controls,¹¹⁻¹⁵ showed as much atrophy in patients with frontotemporal dementia as in patients with Alzheimer's disease.

Older age³⁹ and smaller cranial volume are associated with a smaller quantity of brain tissue. Furthermore, sex is associated with differential brain aging.⁴⁰ Therefore, the normal effect that age, cerebral width, and sex have in elderly controls must all be taken into account to compare measures of atrophy across patient groups. Age has been shown to be the most consistent correlate of brain atrophy in normal elderly subjects,³⁹ and all measures were corrected for age, whereas the correction for cerebral width and sex was applied only to measures in which an association was found in our control group. Bifrontal index ($r = 0.47$; $P = 0.008$), and right ($r = 0.46$; $P = 0.009$) and left ($r = 0.59$; $P = 0.001$) width of the temporal horn were associated with age, whereas interuncal distance ($r = 0.59$; $P < 0.0001$) and right ($r = 0.49$; $P = 0.005$) and left ($r = 0.47$; $P = 0.008$) width of the temporal horn were associated with cerebral width in controls. Correlations of the other measures with age and cerebral width in controls were not significant and ranged between -0.02 and 0.31 , and between -0.11 and 0.23 respectively. Age standardised values were computed for all measures across values of age—that is, correcting the rough measure for the effect of greater atrophy with advancing age (see methods). For interuncal distance and width of the temporal horn, age standardised values were computed also across values of cerebral width. Furthermore, the relation between atrophy and age in controls was different in men and women for the right width of the temporal horn (age $\times$ sex interaction in

Table 3 Rough values of cerebral width and measures of atrophy in patients with frontotemporal dementia (FTD) and Alzheimer's disease (AD), and controls

	FTD (n = 14)	Mild AD (n = 33)	Moderate AD (n = 13)	Controls (n = 31)
Cerebral width	132.5 (7.1)	129.5 (5.6)	134.4 (6.3)	132.9 (6.9)
Bifrontal index	33.3 (3.5)	31.9 (2.6)	31.0 (5.4)	29.0 (2.7)
Interhemispheric fissure width	5.3 (1.9)	5.4 (2.0)	5.0 (1.5)	4.1 (1.5)
Interuncal distance	31.0 (6.3)	30.2 (3.8)	30.1 (4.9)	26.8 (4.0)
Minimum thickness of the MTL:				
Right	14.2 (2.2)	12.3 (3.1)	13.5 (1.7)	14.5 (1.9)
Left	14.8 (3.0)	12.4 (2.1)	10.6 (0.5)	14.7 (1.6)
Smallest*	13.7 (2.4)	11.4 (2.9)	10.6 (2.0)	13.7 (1.5)
Hippocampal height:				
Right	13.9 (2.5)	13.8 (1.8)	13.8 (1.7)	15.5 (1.6)
Left	13.0 (2.3)	12.9 (1.9)	12.9 (3.2)	14.7 (1.3)
Smallest*	12.5 (2.2)	12.6 (1.7)	12.4 (2.6)	14.3 (1.3)
Width of the choroid fissure:				
Right	4.3 (2.0)	4.5 (1.9)	3.9 (1.1)	2.5 (1.1)
Left	4.1 (1.4)	4.4 (1.5)	4.1 (1.7)	2.8 (1.1)
Largest*	4.8 (1.8)	4.8 (1.8)	4.5 (1.4)	3.0 (1.2)
Width of the temporal horn:				
Right	5.1 (2.2)	5.0 (2.1)	6.0 (2.3)	3.1 (1.3)
Left	7.2 (3.6)	6.1 (2.3)	6.5 (1.9)	3.3 (1.1)
Largest*	7.3 (3.5)	6.5 (2.2)	7.2 (2.1)	3.5 (1.2)

Measures are means (SD) in mm except bifrontal index, which is computed as indicated by Barr *et al.*¹⁵ MTL = medial temporal lobe.

*Only right or left values indicating greater atrophy in each patient have been used for computations.

Table 4 Measures of atrophy expressed as multiples of the median in patients with frontotemporal dementia (FTD) and Alzheimer's disease (AD) and controls

	FTD (n = 14)	Mild AD (n = 33)	Moderate AD (n = 13)	Controls (n = 31)	P*	†	‡
Bifrontal index	1.18 (0.13)	1.07 (0.11)	1.06 (0.17)	1.00 (0.08)	0.003	0.05	< 0.0005
Interhemispheric fissure width	1.32 (0.49)	1.28 (0.48)	1.22 (0.39)	1.00 (0.38)	NS	NS	0.02
Interuncal distance	1.18 (0.26)	1.16 (0.15)	1.10 (0.16)	1.00 (0.12)	NS	NS	0.002
Minimum thickness of the MTL (smallest)§	0.93 (0.16)	0.80 (0.19)	0.81 (0.14)	0.94 (0.09)	0.03	0.05	NS
Hippocampal height (smallest)§	0.83 (0.15)	0.83 (0.11)	0.82 (0.16)	0.96 (0.09)	NS	NS	0.001
Width of the choroid fissure (largest)§	1.96 (0.85)	1.77 (0.67)	1.71 (0.50)	1.15 (0.45)	NS	NS	< 0.0005
Width of the temporal horn (largest)§	2.73 (1.62)	2.00 (0.68)	2.22 (0.72)	1.09 (0.29)	0.03	NS	< 0.0005

Measures are mean (SD) of multiples of the median.
P = Significance on *t* test of the difference between FTD and *mild AD, †moderate AD, and ‡controls. Significance values below 0.10 are reported.
MTL = medial temporal lobe; multiples of the median are computed by regressing measures of atrophy on age and cerebral width (interuncal distance and width of the temporal horn) or age alone (all other measures).
§Only right or left values of the multiples of the median indicating greater atrophy in each patient have been used for computations.

Table 5 Discriminant functions separating 14 patients with frontotemporal dementia (FTD) and 46 with Alzheimer's disease (AD), and 31 controls

Actual group	Predicted group membership (no (%))		
	FTD	AD	Control
<i>Algorithmic model</i>			
FTD	11 (79)	1 (7)	2 (14)
AD	10 (17)	28 (61)	8 (22)
Control	0 (0)	4 (13)	27 (87)
1st discriminant function: 2.43*bifrontal index + 0.64* minimum thickness of the MTL - 4.17*hippocampal height + 1.12*width of the temporal horn - 1.50.			
2nd discriminant function: 3.43*bifrontal index + 6.16* minimum thickness of the MTL + 1.77*hippocampal height + 0.23*width of the temporal horn - 11.29.			
<i>Hypothesis driven model</i>			
FTD	11 (79)	0 (0)	3 (21)
AD	10 (17)	28 (61)	8 (22)
Control	0 (0)	2 (6)	29 (94)
1st discriminant function: 3.57*bifrontal index + 2.14* minimum thickness of the MTL + 1.09*width of the temporal horn - 7.65.			
2nd discriminant function: 2.11*bifrontal index + 6.25* minimum thickness of the MTL - 0.08*width of the temporal horn - 7.55.			

MTL = medial temporal lobe.
In the algorithmic model, variables independently maximising the distance between groups were selected on a stepwise selection basis. In the hypothesis driven model measures selected a priori were entered. Variables are entered in the models as multiples of the median (for further details, see methods).

a general factorial ANOVA model: $b = -0.05$; 95% confidence interval -0.09 to -0.01 ; $F_{(1,27)} = 5.90$; $P = 0.02$) indicating that this measure was increasing with Alzheimer's advancing age in male and female controls, but more so in men. For this reason, age standardised values of the right width of the temporal horn were computed separately for men and women.

Table 4 shows measures of atrophy expressed in terms of age standardised values, confirming that all measures except minimum thickness of the medial temporal lobe showed greater atrophy in patients with frontotemporal dementia than in controls. The bifrontal index showed greater atrophy and minimum thickness of the medial temporal lobe indicated lower atrophy in patients with frontotemporal dementia than patients with Alzheimer's disease. Width of the temporal horn showed greater atrophy in patients with frontotemporal dementia than patients with mild Alzheimer's disease. Significance for difference with moderate Alzheimer's disease was not reached.

Table 5 shows discriminant analyses separating patients with frontotemporal dementia from patients with Alzheimer's disease and controls. Two separate models were built, the

first relying on the mathematical properties of the technique of stepwise selection of variables, and the second entering in the model only those variables that were expected to best discriminate groups on the basis of the previously shown data (see methods). The first analysis selected bifrontal index, minimum thickness of the medial temporal lobe, hippocampal height, and width of the temporal horn, achieving sensitivity for detection of frontotemporal dementia around 80%. Eighty seven per cent of controls and only 61% of patients with Alzheimer's disease were correctly classified. Overall, 73% of subjects were correctly classified. The second analysis

Figure 5 Measures of atrophy best discriminating patients with frontotemporal dementia (FTD), patients with Alzheimer's disease (AD), and controls. The thick lines represent the means and the upper and lower borders of boxes represent upper and lower standard deviations. Minimum thickness of the medial temporal lobe and width of the temporal horn are smallest and largest, respectively: only right or left values indicating greater atrophy in each patient have been used for computations.

proved more efficient, increasing specificity of discrimination of frontotemporal dementia from Alzheimer's disease (one patient with frontotemporal dementia previously classified as having Alzheimer's disease was now classified as a control) and sensitivity for classification of controls (two controls previously classified as having Alzheimer's disease were now correctly classified). Overall, 79% of subjects were correctly classified. Figure 5 shows the age standardised values of bifrontal index (A), minimum thickness of the medial temporal lobe (B), and width of the temporal horn (C) in patients with frontotemporal dementia, mild and moderate Alzheimer's disease, and controls.

Discussion

The study shows that patients with frontotemporal dementia have greater atrophy in the anterior brain regions than patients with Alzheimer's disease, that atrophy of the hippocampal formation is present in patients with frontotemporal dementia as well as in patients with Alzheimer's disease, and that the medial temporal lobe is spared in frontotemporal dementia. A pattern of frontal and hippocampal atrophy in the absence of atrophy of the medial temporal lobe might be distinctive of frontotemporal dementia.

The most striking neuropathological features of frontotemporal dementia are gliosis, neuronal loss, and atrophy in the anterior regions of the frontal and temporal lobes.² Although quantitative brain atrophy *in vivo* has never before been evaluated in frontotemporal dementia, it is not surprising that the bifrontal index indicated greater atrophy than in both patients with Alzheimer's disease and controls. Functional neuroimaging with SPECT and HM-PAO or PET showing anterior hypofunction is thought to be supportive of the diagnosis of frontotemporal dementia,^{2-4,6} but specificity is probably low.^{5,41,42} The extent to which brain atrophy contributes to perfusion deficits evidenced by SPECT is debatable,⁴³ but it can be hypothesised that at least part of the frontal hypoperfusion of patients with frontotemporal dementia is due to loss of brain tissue in the anterior regions.

The hippocampus is the first structure to be affected in the course of Alzheimer's disease.⁴⁴ This is in good agreement with the clinical finding of early memory deficits in patients with Alzheimer's disease, and has prompted *in vivo* investigations on the development of hippocampal atrophy in the disease.¹⁷ Recent research has shown that accurate (but elaborate) measurements of hippocampal volumes can differentiate early Alzheimer's disease from controls with a sensitivity and specificity of around 95%,⁸ and that the more feasible linear measures of atrophy of the hippocampal formation also have satisfactory accuracy.^{10,12,14} However, hippocampal atrophy has been reported also in temporal lobe epilepsy and schizophrenia,^{18,19} although memory disturbances are not pre-eminent in these conditions. Hippocampal atrophy has been reported

in pathological studies of frontotemporal dementia.^{45,46} The present data indicate that atrophy of the hippocampal formation can also be seen *in vivo* in frontotemporal dementia, although memory disturbances are characteristically minor.^{1,3,5,6}

Atrophy in the medial temporal lobe has been shown in moderately to severely demented patients with Alzheimer's disease and has been proposed as a sensitive marker of this disease.⁹ It has previously been shown that atrophy of the medial temporal lobe is indeed present in early Alzheimer's disease, but it is less pronounced than atrophy of the hippocampal formation as shown by the width of the temporal horn.^{12,14} Atrophy of the medial temporal lobe was notably absent in our patients with frontotemporal dementia, supporting the view that different subcomponents of the medial temporal lobe structures are involved in Alzheimer's disease and frontotemporal dementia.

In the present study, the rubric of frontotemporal dementia did not include Pick's disease and progressive aphasia.²² Pick's disease is less frequent than frontotemporal dementia (ratio of 1:4).² It can be clinically similar to frontotemporal dementia,^{2,6,21} but is characterised by striking morphological features—namely, frontal and temporal pole atrophy²¹—and distinctive neuropathology.⁴⁵ Therefore, it has been suggested that Pick's disease might represent a nosographic entity distinct from frontotemporal dementia.^{45,47} Frontotemporal dementia, although it can have different pathological patterns,⁴⁵ has much less striking morphological features, which are limited to mild frontal and temporal cortical atrophy.^{2,45} For these reasons, quantitative measurements of atrophy are not useful in the diagnosis of Pick's disease, but are potentially useful in the diagnosis of frontotemporal dementia. Had cases of Pick's disease been included in our frontotemporal dementia sample, it could have been argued that the atrophic changes were an effect due to cases of Pick's disease. Progressive aphasia is a descriptive term with heterogeneous pathology, comprising frontotemporal dementia, and Alzheimer's and Creutzfeldt-Jakob disease.⁴⁸ Thus the inclusion of patients with progressive aphasia with our patients with frontotemporal dementia could have biased the sample.

Measures of atrophy in frontotemporal dementia have been compared with those in two samples of patients with Alzheimer's disease of different severity. Although what is meant by severity in Alzheimer's disease is clear and accepted, this is much less clear for frontotemporal dementia. The MMSE,²³ which is the most used and sensitive indicator of severity in patients with Alzheimer's disease, might not be appropriate in frontotemporal dementia because of the frequent presence of language disturbances. The clinical dementia rating scale,²⁶ on the other hand, is less influenced by language disturbances, but is much less sensitive. As can be seen from table 1, patients with frontotemporal dementia were similar on the clinical dementia rating

scale as patients with mild Alzheimer's disease and similar on the MMSE to patients with moderate Alzheimer's disease. Whatever the definition of severity in frontotemporal dementia, we think that the fact that our findings hold by comparing frontotemporal dementia with two samples of patients with Alzheimer's disease of different severity adds more strength to the results.

Some notes of caution should be considered in the interpretation of these results.

The best results in the discrimination of patients with early Alzheimer's disease from controls have been achieved with volumetric measurements of the hippocampus.⁸ However, linear measures have also been shown to yield good sensitivity and specificity in this discrimination.^{10,12,14} Furthermore, linear measures of hippocampal atrophy have greater feasibility than volumetric measurements.

In this study, patients with frontotemporal dementia were defined on clinical grounds only. However, some findings suggest that they are a distinct clinical entity. Firstly, neuropsychological testing and functional assessment were clearly indicative of relative sparing of daily function and learning, which are among the most striking features of frontotemporal dementia.^{1,3,5,6} Furthermore, visuospatial learning was spared more than verbal learning, and visuospatial abilities are thought to be more preserved than verbal abilities in patients with frontotemporal dementia.^{1,3,5,6} Secondly, the allele $\epsilon 4$ of apolipoprotein E has been consistently shown to be more frequent in patients with Alzheimer's disease than in controls.^{49,50} Patients with mild and moderate Alzheimer's disease had the expected frequency of 0.40–0.50, whereas those with frontotemporal dementia had a much lower frequency of $\epsilon 4$, similar to that found in controls, suggesting that patients with frontotemporal dementia had a disease distinct from Alzheimer's disease. Thirdly, frontal atrophy as measured with the bifrontal index was more pronounced in patients with frontotemporal dementia than patients with Alzheimer's disease. It should be emphasised that the $\epsilon 4$ allele and frontal atrophy were not used to differentiate patients with frontotemporal dementia from patients with Alzheimer's disease, and therefore constitute independent evidence of nosographic autonomy. Lastly, clinical confirmation of the diagnosis of frontotemporal dementia was obtained in all patients after eight to 24 months of follow up, providing further support for the clinical diagnosis.

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