Patterns of Frontal Lobe Atrophy in Frontotemporal Dementia: A Volumetric MRI Study

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Key Words

Frontal variant frontotemporal dementia • Volumetric MRI • Orbitofrontal cortex

Abstract

Objectives: Frontotemporal dementia (FTD), the second commonest degenerative cause of dementia under the age of 65, often presents with striking changes in behaviour and personality in association with frontal lobe atrophy. Based on the behavioural changes observed in FTD, it is commonly assumed that the orbitofrontal cortex is the earliest and most severely affected frontal sub-region. However, evidence to support this assumption has to date been largely lacking. **Methods:** Using a novel volumetric MRI method, we performed a detailed volumetric analysis of six frontal regions in 12 subjects with the frontal or behavioural variant of FTD (fvFTD) and 12 age-, education- and sex-matched normal controls. The regions studied were: the orbitofrontal and insula regions (representing the orbitobasal cortex); the inferior and middle frontal regions (representing the dorso-lateral prefrontal areas); and the superior frontal and ante-

rior cingulate regions (representing the medial prefrontal areas). **Results:** As a group, the fvFTD patients showed atrophy involving all six regions. We then segregated the 12 patients into three sub-groups according to their overall degree of atrophy. In the mildest group (n = 3) all regions fell within 2 standard deviations of normal. In the intermediate group (n = 6) only the orbitofrontal region (bilaterally) fell clearly outside the control range (>2 z scores below the control mean); the next most atrophic region in this group was the right insular region. The severe group (n = 3) had generalized atrophy throughout the frontal regions measured. **Conclusions:** In conclusion, patients with the earliest stages of fvFTD show no significant loss of volume in any frontal lobe area as measured by a novel MRI volumetric technique. When volume loss does occur, changes are initially seen in the orbitofrontal cortex before atrophy becomes more widespread. These results provide some partial support for the often-quoted assumption that the orbitofrontal cortex is the locus of earliest pathology in fvFTD, although these findings must be regarded as preliminary in view of the small numbers of patients involved.

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Introduction

Frontotemporal dementia (FTD) is the term now preferred for the group of non-Alzheimer neurodegenerative diseases that present with focal cognitive deficits arising from circumscribed pathology of the frontal and/or temporal lobes [1, 2]. Three main clinical presentations of FTD are recognized: the frontal or behavioural variant of frontotemporal dementia, termed fvFTD, in which the initial clinical picture is of behavioural and personality changes; semantic dementia, in which the initial presentation is a fluent anomia and impaired comprehension secondary to loss of semantic knowledge, and progressive non-fluent aphasia, in which the predominant impairment is a profound impairment of expressive language. A feature of early fvFTD is the flawless performance, of some subjects, on standard neuropsychological tests while concurrently manifesting changes in social behaviour that severely disrupt their working and family life. Such behavioural changes include the development of stereotypical or ritualized behaviours, a change in food preference for sweet things, increasing apathy and/or disinhibition, a loss of empathy, and an almost universal loss of insight [3, 4]. These changes may predate neuropsychological deficits by several years [5], and thus a major challenge is to develop better methods of early, accurate detection in fvFTD.

As standard neuropsychological testing may be insensitive to early fvFTD, attention has focussed on the development of behavioural measures. Standardized carer interviews such as the Neuropsychiatric Inventory [6], which appears to differentiate patients with FTD and Alzheimer's disease [7], and the Frontal Behaviour Inventory, which appears to discriminate patients with FTD from those with Alzheimer's disease or depression [8–10] have been undoubted advances in the area. More recent work has focussed on specific behaviours, such as changes in appetite, food preferences, and eating habits [11], or the presence of stereotypies [12]. The development of experimental neuropsychological tasks sensitive to orbital and mesial frontal function has also begun with paradigms designed to detect difficulties with decision-making, probability and gambling [13], emotion processing [14, 15] and 'theory of mind' [16]. However, although behavioural measures and novel neuropsychological tasks may demonstrate differences between groups of patients with fvFTD and other neurodegenerative diseases, none are reliable enough to serve as a diagnostic tool in individual cases.

With this in mind, both functional and structural neuroimaging have been explored as aids to early diagnosis of fvFTD. Based on the behavioural changes seen in fvFTD, it is commonly assumed that the orbital and medial frontal cortex is the earliest and most severely affected frontal sub-region, but in fact evidence to support this assumption is largely lacking. Studies using functional neuroimaging have claimed that frontal lobe hypoperfusion seen on single photon emission computerized tomography (SPECT) scanning is sensitive and specific to FTD [17–19], but some authors have pointed out that such hypoperfusion was often used as an inclusion criterion to studies and that longitudinal follow-up of subjects demonstrates that SPECT scans can be initially normal in fvFTD [5].

With regard to structural imaging, patients with fvFTD often present with MR images that are normal to visual inspection despite marked behavioural changes. One approach to this problem has been to use the technique of voxel-based morphometry (VBM), which can identify differences between a target brain and a template of pooled normal control brains on a voxel-by-voxel basis. In the only published study to date of VBM in fvFTD, 8 fvFTD patients were compared with 12 patients with semantic dementia and a group of matched controls [20]. Regions of significant atrophy seen in both clinical groups were located in the ventromedial frontal cortex, the posterior orbital frontal regions bilaterally, the insula bilaterally, and the left anterior cingulate cortex. The fvFTD group additionally showed atrophy in the right dorsolateral frontal cortex and the left premotor cortex. There are, however, methodological issues with the technique of VBM, particularly where there is severe volume loss or the structure under examination is small. For example, a previous VBM study of 6 patients with semantic dementia found no evidence of hippocampal atrophy [21], although two subsequent volumetric studies both found hippocampal atrophy in semantic dementia that was at least as severe as that seen in Alzheimer's disease [22, 23].

One question is therefore whether the subtle degrees of atrophy seen in the early stages of fvFTD can be better detected by volumetric MRI analysis. Quantitative MRI techniques using volumetric measurements of regions of interest certainly show greater sensitivity to areas of focal atrophy than visual inspection in early Alzheimer's disease [24–26] and in semantic dementia (as above), but data in fvFTD are lacking.

An additional question is whether specific areas within the frontal lobes undergo earlier or greater rates of at-

rophy. A segregated organization of function within the frontal lobes that has emerged from cytoarchitectonic, functional imaging and lesion studies [27–32] suggests particular behaviours in FTD may be related to pathological involvement of specific prefrontal areas. One proposal is that the lateral prefrontal cortex supports executive functioning, the medial prefrontal areas mediate motivation and drive and the orbitobasal cortex is concerned with aspects of social behaviour [28, 32]. In order to examine these specific regions of interest, we based our division of the frontal lobes into six regions: the orbitofrontal and insula regions (representing the orbitobasal cortex); the inferior and middle frontal regions (representing the dorsolateral prefrontal areas); and the superior frontal and anterior cingulate regions (representing the medial prefrontal areas). Based upon the predominance of changes in social behaviour we hypothesized that the orbitofrontal/insula sub-regions were likely to show the greatest and earliest atrophy in fvFTD.

Methods

Subjects

A total of 24 subjects participated: 12 with fvFTD and 12 age-, education-, and sex-matched controls. Patients were selected from those undergoing longitudinal evaluation at the University of Cambridge Neurology unit. All patients were assessed by a neurologist, neuropsychologist, and psychiatrist and were excluded if they had a history of known or suspected cerebral ischemic event, alcohol abuse, head injury, other major medical illness or if there was a past history of depressive illness. The diagnosis of FTD was made on clinical grounds in keeping with international consensus criteria for FTD [2]. All patients had presented with a history of progressive change in personality and behaviour with at least five of the following features: loss of insight, disinhibition, apathy, restlessness, emotional lability, distractibility, reduced empathy, lack of foresight, poor planning, impulsiveness, social withdrawal, poor self-care, reduced verbal output, verbal stereotypes or echolalia, perseveration, poor self-care or features of the Kluver-Bucy syndrome. Progression was assessed clinically in terms of changes in functional abilities (e.g. job performance), the development of more of the behavioural features listed above, or deterioration in neuropsychological performance. In keeping with prior studies from Cambridge, we have used the label fvFTD to designate this behavioural variant of FTD as distinct from the language variants of FTD (semantic dementia and progressive non-fluent aphasia).

Controls were healthy volunteers selected from the subject panel at the MRC Cognition and Brain Science Unit. Control subjects were excluded if they had a history of alcoholism, substance abuse, major head injury, epilepsy, or other neurological disorders.

Mean (standard deviation) ages in years were, for the patients with fvFTD, 57.5 (5.4); and for the control participants, 60.1 (3.8) (Mann-Whitney U, n.s.). For the patients with fvFTD, mean

(standard deviation) scores on screening cognitive and behavioural measures were as follows: on the Mini Mental State Examination (MMSE), 24.0 (7.3); on the Addenbrooke's Cognitive Examination (ACE), 71.2 (25.0); and on the Cambridge Behavioural Inventory (CBI), 123.8 (42.3).

Imaging

MRI Acquisition. MRI scanning was performed on a 1.5-tesla Signa MRI scanner (GE Medical Systems, Milwaukee, Wisc., USA). In all subjects, MR images of the entire brain were obtained using a three-dimensional, inversion recovery prepared, fast-gradient echo sequence with the following settings: repetition time = 13.5 ms, echo time = 4.2 ms, inversion time = 650 ms, field of view = 22 cm, slice thickness = 1.5 mm, matrix 256×256 . Slice number was chosen to encompass the whole brain and varied between 116 and 124 slices. Total acquisition time was approximately 9 min. After acquisition brains were spatially normalized using Analyze software so that the anterior-posterior axis was realigned parallel to the anterior-posterior commissure (AC-PC) line and the interhemispheric fissure was aligned on the other two axes.

MRI Volumetric Analysis. Tissue volumes were determined by a single rater (R.J.P.) who was blind to the subjects' details at the time of volumetric assessment and had not been involved in their prior clinical assessment. Regions of interest were manually traced on a Sun Sparcstation (Sun Microsystems, San Francisco, Calif., USA) using Analyze (Biomedical Imaging Resource, Mayo Clinic, Rochester, Minn., USA), Voxblast (Image Analysis Facility, University of Iowa, Vaytek Inc, Fairfield, Iowa, USA) and in-house software. Image processing consisted of stripping the skull from the images to create a brain volume that could be simultaneously viewed in a multiplanar 3-D and 2-D display. Boundaries for regions of interest were defined using a standard brain atlas [33] and were delineated and marked using a combination of brain surface markings on the 3-D volume and concurrent multiplanar 2-D views. Regions of interest were traced using a mouse-driven cursor on T_1 -weighted coronal images and included: orbitofrontal, insula, inferior frontal, middle frontal, superior frontal, and anterior cingulate regions. All regional volumes were corrected for total intracranial volume (TICV) measured using T_2 axial images and including all tissue rostral to the opening of the medulla. A segmentation process was used to produce a separate total CSF and total brain volume to give measures of total cerebral atrophy.

Intrarater reliability was assessed by repeated measurements of five of the subject scans. The coefficient of reliability [34], a measure of the observed disagreement/chance expected disagreement, was >0.95 for all regions.

Techniques for measuring the individual frontal lobe regions are outlined below using anatomical landmarks defined with reference to a standard brain atlas [33]. Central to the division of the frontal lobes into different regions was the use of a 'wheel and spoke' method [35], which uses a reference point that acts as the hub or spindle of the wheel. This reference point was taken to be the midpoint of the lateral border of the lateral ventricle for the orbitofrontal and insula regions, the most lateral point of the lateral ventricle for the inferior frontal region, and the most superior point of the lateral ventricle for the middle frontal, superior frontal and anterior cingulate regions (fig. 1 and 2). For slices anterior to the lateral ventricles, the reference point was a spindle

Fig. 1. Schematic of the six frontal regions: cross-sectional, coronal view.

extended from the most anterior point of the lateral ventricle to the frontal pole. The anterior boundary for the orbitofrontal, inferior frontal, middle frontal and superior frontal regions was the first slice on the coronal images in which the olfactory sulcus was seen. The posterior boundary for the above regions and the anterior cingulate region was the last slice before the closure of the optic chiasm, and for the insula region the slice on which the anterior commissure was most clearly seen.

Techniques for Measurement of Individual Regions

Orbitofrontal Region. The reference point for the orbitofrontal region was taken to be the midpoint of the lateral border of the lateral ventricle and for the slices anterior to the appearance of the lateral ventricle, the central spindle. The supero-lateral border of the orbitofrontal region was defined on the 3-D images using surface drawn arcs connecting the frontal pole, the most posterior point of the lateral orbital sulcus (LOS), and the inferior margin of the circular sulcus of the insula [36]. The lateral orbital sulcus is the most lateral and ventral sulcus below the horizontal ramus of the lateral fissure and was identified on coronal images and cross-referenced to the 3-D surface images. The medial border on anterior slices was defined by a horizontal line drawn from the spindle to the medial surface of the frontal lobe. Moving caudally, the medial border was defined by the inferior border of the cingulate region until the appearance of the corpus callosum. On more posterior slices, the medial border extended as far as the inferior aspect of the genu of the corpus callosum. In terms of cytoarchitectonic areas, this region is thought to include Brodman areas 11, 13, 14, 15, 25, the medial portion of 12, and the infracallosal portion of area 32.

Insula Region. The insula region was determined from both sagittal and coronal sections of the brain. The most anterior aspect of the insula was marked on the sagittal images. The superior and inferior boundaries were marked by the circular sulcus of the insula. The reference point for the insula region was the midpoint of the lateral border of the lateral ventricle. The insula region was traced back to the slice on which the anterior commissure was seen most clearly.

Inferior Frontal Region. This area corresponds to the inferior frontal gyrus and is thought to predominantly incorporate Brodman areas 44, 45, but also include parts of 46 and 47. The reference point was taken to be the supero-lateral point of the lateral ventricle where present and for the slices anterior to the appearance of the lateral ventricle, the central spindle. The surface landmarks that form the boundary for this area correspond to the inferior frontal sulcus (IFS) superiorly and the superior border of the orbitofrontal region inferiorly. Although the IFS was readily identifiable in all subjects, we found considerable variation in both its course and our ability to reliably identify it on all slices. Because of this, we adopted a template approach in which a 'standard IFS' was calculated. The standard IFS was first calculated from averaging the position of the IFS on the brain images of 10 subjects. The standard IFS measurements were then applied to each subject's brain to mark the IFS for that subject. To create the template, the position of the inferior frontal sulcus was marked on two separate slices of the coronal images; the first slice at which the genu of the corpus callosum was visible, and the last slice to be traced at the level of the closure of the optic chiasm. The angle that each of these points subtended to a vertical line drawn through the interhemispheric fissure was then calculated and averaged across the 10 subjects. The inferior frontal

Fig. 2. Schematic of the six frontal regions: surface anatomy.

sulcus subtended an average angle of 70° to the vertical at the first slice at which the genu of the corpus callosum was seen and 66° at the last slice before the closure of the optic chiasm.

For each brain to be measured, markings for the IFS were made on the brain surface at the corresponding angles. These points were then connected by a surface arc drawn on the 3-D surface rendered images.

Middle Frontal Region. This area corresponds to the middle frontal gyrus and to the lateral parts of Brodman areas 6, 8, and 9. The reference point was the same as for the inferior frontal region. The surface boundaries of this area correspond to the inferior and superior frontal sulci. The position of the superior frontal sulcus was calculated and marked using the same template method used in marking the inferior frontal sulcus. The superior frontal sulcus subtended an average angle of 38° at the callosal slice and 34° at the optic chiasmatic slice.

Superior Frontal Region. This area corresponds to the superior frontal gyrus and the lateral parts of Brodman areas 6, 8, and 9. The reference point was the same as for the inferior and middle frontal regions. The supero-lateral border is defined by the superior frontal sulcus marked as above and the medial border as formed by the superior extent of the cingulate region.

Cingulate Region. This area corresponds to Brodman area 24 and supracallosal parts of area 32. There is substantial variability in the sulcal pattern on the medial surface of the brain with the cingulate sulcus showing a double parallel distribution in around 35% of cases. Rather than use the cingulate sulcus, the inferior, anterior, and superior borders of the cingulate region were defined on sagittal images by a line drawn onto the medial surface of the brain, halfway between the corpus callosum and the brain

surface. On slices posterior to the genu of the corpus callosum, only the area superior to the corpus callosum was included in the cingulate region.

Results

Total and Regional Brain Volumes

Table 1 shows the corrected values for the total intracranial volume (TICV), total brain volume, and individual volumes of the combined grey and white matter of the six frontal sub regions. Before analysis of variance calculations, Levene's test of homogeneity of variance was applied to test that the two groups came from populations with equal variance. The Levene statistic was non-significant for all of the variables measured. ANOVA calculations showed no significant difference in age between the two groups ($F(1,22) = 1.50, p = 0.23$) and no significant difference in TICV ($F(1,22) = 1.77, p = 0.19$) between the patient and control groups. There were, however, highly significant differences between the FTD and control groups in both total brain volume (TBV) and all six regional volumes, right and left. The same results were obtained with a non-parametric method (Mann-Whitney U), summarized in table 1.

Table 1. Summary data and mean regional volumes in patients and controls

	Control subjects (n = 12)		fvFTD patients (n = 12)		p
	mean	SD	mean	SD	
General measures					
Age, years	60.2	3.8	57.8	5.6	n.s.
TICV, cm ³	1,437.5	128.7	1,507.0	128.5	n.s.
TBV, cm ³	1,361.4	47.5	1,241.6	90.5	<0.001
Regional volumes, cm ³					
R orbitofrontal	25.5	2.0	18.8	4.0	<0.001
L orbitofrontal	26.2	2.5	18.4	3.8	<0.001
R insula	4.4	0.5	3.2	1.2	<0.005
L insula	4.1	0.8	3.2	0.9	<0.05
R inferior frontal	25.3	4.3	18.9	3.8	<0.001
L inferior frontal	23.1	3.9	18.0	2.7	<0.001
R middle frontal	19.3	2.6	14.3	2.9	<0.001
L middle frontal	17.9	2.5	13.1	2.8	<0.001
R superior frontal	27.5	4.1	19.8	5.4	<0.001
L superior frontal	26.7	5.2	18.3	5.2	<0.001
R cingulate	6.7	1.1	5.0	1.6	<0.01
L cingulate	7.2	1.2	5.1	1.5	<0.001

fvFTD = Frontal variant frontotemporal dementia; SD = standard deviation; TICV = total intracranial volume; TBV = total brain volume; n.s. = not significant.

To examine the effects of disease stage the patients were divided into three groups based upon their overall degree of frontal atrophy: 3 had overall frontal volumes within two z scores of normal; 6 had overall frontal volumes between 2 and 4 z scores below normal, and 3 had overall frontal volumes greater than 4 z scores below normal. Significant atrophy was defined as a mean regional volume more than two z scores below the control mean. In the mild group, no regions were significantly atrophic; in the moderate group, only the orbitofrontal region was clearly affected; and in the severe sub-group all regions showed significant involvement, although orbitofrontal atrophy continued to predominate (fig. 3a–c, respectively).

One caveat regarding this finding is that as orbitofrontal volume is included within total frontal volume, the measures are confounded. On re-ranking, however, by the residual of total frontal volume minus total orbitofrontal volume, patients fell into exactly the same groups of mild (n = 3), moderate (n = 6) and severe (n = 3) atrophy.

Correlation of Total and Regional Brain Volumes with Cognitive and Behavioural Data

Mean and standard deviation age in years, MMSE, ACE and CBI scores are presented for the three groups of patients (mild, moderate, and severe atrophy) in table 2.

As can be seen, greater frontal atrophy was associated with older age; greater impairment on both the MMSE and ACE; and a higher score for behavioural disturbance on the CBI. However, correlations between measures of frontal and orbitofrontal volume (total frontal volume; total frontal volume minus orbitofrontal volume, and orbitofrontal volume alone) and age in years, impairment on the MMSE and ACE, and score on the CBI fell below significance in all cases (Spearman's rho, n.s.). To examine the data in more detail, patients were divided into two groups on the basis of a median split on the three volume measures outlined above. The performance of each split group was then compared on the ACE as a screening measure of cognitive function, and the CBI as a measure of behavioural disturbance. Low total frontal volume and total frontal volume minus orbitofrontal volume were both significantly associated with greater impairment on the ACE (Mann-Whitney U, $p < 0.05$), but not significantly associated with a higher score on the CBI. Low orbitofrontal volume, however, was not significantly associated with greater impairment on the ACE or a higher score on the CBI, although CBI scores were lacking in two highly behaviourally disturbed patients in the severe frontal atrophy group.

Fig. 3. Mean regional volumes by patient subgroup: mild atrophy (n = 3) (a), moderate atrophy (n = 6) (b), and severe atrophy (n = 3) (c). Values are expressed in z scores derived from control mean and standard deviation values. Error bars indicate plus or minus two standard errors of the mean.

Table 2. Age, MMSE, ACE and CBI scores for patients with mild (n = 3), moderate (n = 6), and severe (n = 3) frontal atrophy

	Mild		Moderate		Severe	
	mean	SD	mean	SD	mean	SD
Age, years	52.1	2.4	58.8	5.9	60.4	4.1
MMSE/30	27.7	0.6	23.2	8.6	22.0	8.9
ACE/100	87.3	9.9	67.8	27.9	62.0	29.1
CBI/324	107.0	39.2	131.2	47.7	178.0 ^a	–

SD = Standard deviation; MMSE = Mini Mental State Examination; ACE = Addenbrooke's Cognitive Examination; CBI = Cambridge Behavioural Inventory.

^a CBI score only available for 1 of 3 patients in the severe frontal atrophy group.

Survival and Pathology

The volumetric analyses were performed on MRI scans obtained in 1999 and 2000. Subsequently, 8 of the 12 patients have died. All 3 patients in the mildest group are alive and remain under follow-up, although their dementia has progressed. Five of the 6 patients in the moderate group have died, as have all 3 patients in the severe group. Post-mortem examination of brain tissue was performed in 7 of the 8 deceased patients. Pathology in the 5 deceased patients in the moderate group showed Pick-body-positive Pick's disease in 2, FTD with ubiquitinated inclusions in 1, tau-positive FTD of the corticobasal degeneration type in 1 and no distinctive histology in 1. Of the 3 patients in the severe group, 1 showed no distinctive histology, 1 showed gross frontal lobe atrophy on macro-

scopic examination at post-mortem, but brain tissue was not examined microscopically, and 1 did not undergo brain examination.

Discussion

Although it is commonly stated that fvFTD differentially involves the orbitofrontal cortex, evidence to support this statement has been largely lacking. We have now provided partial support for this assumption, although our results should be regarded as strictly preliminary. As a group, our 12 patients showed global atrophy involving all sub-regions of the frontal lobes. There was, however, considerable heterogeneity, with the brains of some patients showing gross atrophy while others appeared normal to visual inspection. To capture this variability, and explore the potential progression of changes, we sub-divided our 12 cases according to their overall degree of atrophy. Of note was the fact that the 3 mildest patients (all of whom had the behavioural hallmarks of fvFTD) showed normal regional frontal volumes. A group of 6 patients with a moderate degree of atrophy (between 2 and 4 z scores below normal) were in many ways the most revealing sub-group since they demonstrated significant atrophy of the orbitofrontal region and right insular region only. The severe sub-group ($n = 3$) had diffuse frontal lobe atrophy.

The findings in the first 3 patients suggest that behavioural changes in fvFTD precede brain atrophy even as judged by detailed volume analysis. Such patients have, we assume, functional disruption of frontal lobe regions that might be revealed by metabolic brain imaging (e.g. FDG-PET), or functional MRI. An alternative interpretation, given the lack of pathological confirmation in this group, is that these patients may fulfil criteria for fvFTD but do not in fact have a degenerative brain disease. Against this view is the fact that these patients have clearly progressed clinically in the subsequent 5 years. Unfortunately, many of our patients with slowly progressive behavioural disturbance (including those in this study) have so far declined repeated MRI imaging to confirm corresponding progression in brain atrophy, but follow-up, re-imaging and recruitment into brain tissue donation programmes for such patients is a current priority. At present, therefore, the place for quantitative MRI in the early diagnosis of individual patients with fvFTD is uncertain, particularly given the labour-intensive demands of the technique, but its role could expand depending on the results of future longitudinal studies.

When atrophy is first measurable, however, it certainly appears to most markedly involve the orbitofrontal cortex. These findings are broadly in keeping with those of Rosen et al. [37], who demonstrated, using voxel-based morphometry, focal grey matter loss in the ventromedial, orbital, insular, anterior cingulate and dorsolateral prefrontal cortices in patients with fvFTD. However, Rosen et al. did not attempt to divide their 8 individuals into sub-groups and were not able therefore to conclude which regions were first affected. More severely affected patients showed generalized frontal cortical atrophy, which was significantly associated with more severe impairment on a screening measure of cognitive function, the ACE.

Of the behavioural features of FTD, disinhibition, stereotypic and ritualized behaviours, alterations in satiety and food preference and impaired emotional judgements have been linked to the orbitofrontal cortex [11, 15, 38]. One of the key cognitive deficits underlying the change in social behaviour is the inability to take the perspective of others, so-called theory of mind [16]. A deficit in theory of mind has also been linked to orbital frontal pathology [39], although other studies implicate more mesial regions. It was not possible in this study, however, to demonstrate a clear association between orbitofrontal cortex atrophy and behavioural disturbance as measured by the CBI. Reasons for this failure include the relatively small numbers of patients, lack of objective behavioural ratings in the most severely affected patients, and the inherent problems of a carer-based rating scale such as the CBI where assessments are made by a different individual for each patient. Recruiting a larger number of moderately affected patients, and rigorously collecting a greater range of both carer-based and objective behavioural data would undoubtedly be of value in further exploring this relationship.

Finally, one of the problems in interpreting our findings relates to the inherent differences in volumes of different frontal regions. For instance, the insular cortex is only a fifth of the size of the orbitofrontal, inferior and superior frontal regions. The cingulate is also a small region in absolute terms. These differences make it relatively more difficult to detect consistent alterations in volume across regions and the lack of change in the smaller regions (notably the insula and anterior cingulate) should, therefore, be interpreted with caution. Differences in opinion also exist, of course, as to where the boundaries for these anatomical regions should be drawn.

In conclusion, 3 patients with the earliest stages of fvFTD showed no significant loss of volume in any fron-

tal lobe area as measured by a novel MRI volumetric technique. When volume loss did occur, changes were seen predominantly in the orbitofrontal cortex before atrophy became more widespread. These results provide some partial support for the often-quoted assumption that the orbitofrontal cortex is the locus of earliest pathology in fvFTD, although these results should be regarded as strictly preliminary. It is tempting to suggest in turn that many of the clinical features of early fvFTD are a direct consequence of such orbitofrontal underfunction or atrophy, but given the difficulties in accurately measuring atrophy in other frontal brain regions, and the lack of orbitofrontal atrophy in the minimally affected group, that

conclusion may also be premature. It would perhaps be more accurate to suggest that behavioural disturbance in fvFTD reflects disruption of an integrated circuit including the orbitofrontal, insular and mesial frontal lobes, and that orbitofrontal atrophy may be an early, but not invariable indicator of such disruption.

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