

Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype

C. M. Kipps,^{1,2} J. R. Hodges,^{2,3} T. D. Fryer⁴ and P. J. Nestor²

1 Wessex Neurological Centre, Southampton University NHS Trust, Southampton, UK

2 Department of Clinical Neuroscience, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

3 Prince of Wales Medical Research Institute, Randwick, NSW, 2031, Australia

4 Wolfson Brain Imaging Centre, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Correspondence to: Prof. J. R. Hodges,
Prince of Wales Medical Research Institute,
Randwick 2031, NSW,
Australia
E-mail: j.hodges@powmri.edu.au

In patients with the behavioural variant of frontotemporal dementia, prognosis is often surprisingly good when there is normal structural imaging at presentation. Imaging abnormalities are not, however, mandatory for diagnosis, which in the absence of suitable biomarkers, remains entirely clinical. We aimed to test whether cases with normal structural imaging have hypometabolism suggestive of underlying neurodegeneration, or whether it is likely that such patients are false positive diagnoses of behavioural variant frontotemporal dementia. Patients with this disease ($n=24$) and age-matched controls ($n=12$) underwent both magnetic resonance imaging (MRI) and quantitative fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, together with clinical and behavioural assessments. Regions of interest were used to calculate metabolic rate in frontotemporal and control regions. Using a semi-quantitative visual rating scale, patients were divided into MRI-abnormal ($n=15$) and MRI-normal groups ($n=9$). There was definite frontotemporal hypometabolism in the MRI-abnormal group (particularly in the mesial and orbitofrontal regions) even after accounting for brain volume loss, whereas the MRI-normal group was similar to controls in all regions. In contrast, cognitive and behavioural indices did not separate the two behavioural variant frontotemporal dementia patient groups. The results suggest that the clinical syndrome of the behavioural variant of frontotemporal dementia may not be specific for a neurodegenerative disease, and we hypothesize the existence of a phenocopy. A number of alternative neuropsychiatric and developmental explanations are discussed. We advise caution in diagnosing the illness in patients without imaging abnormalities, and propose that imaging findings are included in criteria for diagnosis.

Keywords: frontotemporal dementia; FDG-PET; MRI; social cognition; Pick's disease

Abbreviations: ACE = Addenbrooke's Cognitive Examination; CBI = Cambridge Behavioural Inventory; CDR = Clinical Dementia Rating; FDG-PET = fluorodeoxyglucose-positron emission tomography; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory

Introduction

While awareness of frontotemporal dementia as an important cause of early onset dementia is improving, the specificity of accepted clinical diagnostic criteria remains unclear (Brun *et al.*, 1994; Neary *et al.*, 1998; McKhann *et al.*, 2001). In particular, the status of imaging investigations is uncertain; at present, changes in frontotemporal regions are supportive, but not mandatory for a diagnosis (Neary *et al.*, 1998). In the absence of a reliable biomarker of disease, these issues have important implications for diagnostic accuracy and prognosis, particularly early in the disease.

The clinical classification of patients with frontotemporal dementia is divided into those presenting with insidious alterations in personality and social conduct (behavioural variant frontotemporal dementia) versus those with progressive decline in language abilities: semantic dementia and progressive non-fluent aphasia (Neary *et al.*, 1998). A recent magnetic resonance imaging (MRI) study highlighted the frequency of normal structural imaging in clinically diagnosed behavioural variant frontotemporal dementia, in contrast to patients with semantic dementia in whom a scan was always abnormal at diagnosis (Kipps *et al.*, 2007a). Although the prognosis of frontotemporal dementia is very poor overall, with a median survival of only 6 years (Hodges *et al.*, 2003), and patients with normal imaging have markedly better survival than their imaging-abnormal counterparts (Davies *et al.*, 2006). The delineation of a group of patients with apparent behavioural variant frontotemporal dementia on clinical grounds but with normal structural imaging and a good prognosis raises two possibilities: first that an indolent variant of behavioural variant frontotemporal dementia might exist or, second, that these subjects might represent a false-positive diagnosis.

(¹⁸F)-2-fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) is a sensitive marker of neuronal dysfunction, and can detect regional brain dysfunction, even early in the course of neurodegenerative disease (Nestor *et al.*, 2004; Ciarmiello *et al.*, 2006). A number of studies have described the role of functional imaging using both FDG-PET and single photon emission computed tomography (SPECT) in the diagnosis of behavioural variant frontotemporal dementia (Knopman *et al.*, 2005; Foster *et al.*, 2007; McNeill *et al.*, 2007). These studies were derived retrospectively from autopsy-confirmed data, and demonstrate the potential utility of functional imaging in diagnosing this disease and distinguishing it from Alzheimer's disease and other dementias. They cannot, however, address the possibility of false-positive diagnoses at first presentation because such subjects would be excluded *a priori*. This problem was exemplified in a study of progression of FDG-PET changes in behavioural variant frontotemporal dementia that excluded three clinically diagnosed patients on the grounds of normal PET imaging at baseline (Diehl-Schmid *et al.*, 2007). Interestingly, one of these excluded patients came to post-mortem and was not found to have any neuropathology. Similarly, reports of a patient diagnosed with apparent behavioural variant frontotemporal dementia, who showed no evidence of deterioration over a decade and whose structural and metabolic imaging remained normal throughout that time raises the alternate

possibility of a non-neurodegenerative 'phenocopy' of the syndrome (Kipps *et al.*, 2007b).

An alternate explanation of the structural data might be that the rate of disease progression in frontotemporal dementia is heterogeneous, and that patients with abnormal MRI scans are at the more aggressive end of the spectrum, whereas some with a normal structural scan have more indolent disease. If so, perhaps not all frontotemporal dementia pathologies produce regional volume loss detectable by MRI, but abnormalities could be detectable using a sensitive imaging method such as FDG-PET.

To explore these possibilities we used both functional and structural imaging to assess a large group of patients with a clinical diagnosis of behavioural variant frontotemporal dementia. We compared patients with, and without, structural MRI abnormalities and hypothesized that cases with normal MRI scans would not show abnormalities suggestive of neurodegeneration on FDG-PET, and that since the key diagnostic information in behavioural variant frontotemporal dementia is obtained from an informant, that subjective clinical features may give rise to false positive diagnoses. In addition, we hypothesized that there would be metabolic heterogeneity within the prefrontal cortex, with marked impairments in the medial and orbitofrontal regions, relative to dorsolateral prefrontal or parietal regions which would be in keeping with the predicted regional spread of pathology from post-mortem studies (Broe *et al.*, 2003; Kril *et al.*, 2005).

Methods

Subjects

Patients with behavioural variant frontotemporal dementia diagnosed clinically according to accepted criteria (Brun *et al.*, 1994; Neary *et al.*, 1998) ($n=24$), and appropriate age-matched controls ($n=12$) were recruited from the Addenbrooke's Hospital Memory Clinic, Cambridge between 1999 and 2005. Each patient was assessed by an experienced behavioural neurologist (J.R.H.), a psychiatrist, a clinical psychologist and neuropsychiatrist. No clinical presentation was felt to be due to psychiatric illness. In particular, the clinical features did not reach criteria for major depression, schizophrenia, alcohol, substance abuse or personality disorder. There was no history of stroke or significant head injury. Detailed interviews were conducted with spouses and all reported insidious changes over the previous few years that represented a distinct change from earlier functioning. As described below, all patients obtained high scores on the Neuropsychiatric Inventory (NPI), with a profile typical of behavioural variant frontotemporal dementia. While structural imaging was often supportive of the diagnosis, absence of discernable brain atrophy on magnetic resonance scans was not an exclusion criterion for the diagnosis. We attempted to recruit all recently diagnosed and newly presenting cases over a 6-year period. A total of 12 patients were excluded because of either extreme behavioural disturbance, co-existent medical disorders which precluded MRI (pacemakers) or PET scanning (diabetes) or claustrophobia. No patient had significant vascular lesion load on review of their clinical imaging. Controls were either spouses or were recruited from local community groups. They were screened by a neurologist to ensure that there was no evidence of memory impairment, dementia or other neurological or major psychiatric illness.

Written informed consent was obtained from both subjects and their carers after detailed explanation of the procedures involved. The study was approved by the local regional ethics committee (LREC) and the Administration of Radioactive Substances Advisory Committee (ARSAC), UK.

Imaging

All subjects underwent MRI scanning and FDG-PET scanning.

PET scanning

The acquisition procedure has been described in detail elsewhere (Nestor *et al.*, 2003b). Briefly, fasting (minimum 8 h) FDG-PET scans were performed on a General Electric Advance system in three-dimensional mode, with voxel size $2.34 \times 2.34 \times 4.25$ mm and a field of view of $30 \times 30 \times 15.3$ cm. FDG (74 MBq) was administered and arterial sampling used to calculate the input function. Images were reconstructed using the PROMIS algorithm (Kinahan and Rogers, 1989), with corrections applied for attenuation, dead time, scatter and random coincidences. Cerebral metabolic rate for glucose was calculated from the image and blood data using the Huang autoradiographic technique (Phelps *et al.*, 1979). In the first instance, as there is no validated reference region in frontotemporal dementia, raw cerebral metabolic rate for glucose values (mmol/dl/min) were contrasted; a second analysis in which these values were normalized to the cerebellum was subsequently undertaken to reduce the variance due to normal inter-subject variability in brain metabolism (cerebellar metabolic rate values were similar between the three groups).

MRI scanning

Volumetric MRI scans were obtained with each PET scan and were performed on either a 3-T Bruker system or a 1.5-T GE Signa MRI scanner (GE Medical Systems, Milwaukee, WI). The scanning parameters were as follows: *Bruker*—a T_1 -weighted, three-dimensional, spoiled gradient echo sequence volumetric MRI. The field of view was $25.6 \times 22.0 \times 18.0$ cm with a matrix size of $256 \times 256 \times 256$. *GE Signa*—a three-dimensional, spoiled gradient echo sequence volumetric MRI was acquired with matrix size of $256 \times 256 \times 120$. All MRI scans were resliced using cubic spline interpolation to an isotropic voxel size of 1 mm^3 using Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). Before combining 1.5 T and 3 T data for the PET study, a preliminary analysis of 17 subjects that had both 1.5 T and 3 T MRI ($n=8$ patients, $n=9$ controls) was undertaken. This showed that the mean absolute percentage difference in cerebral metabolic rate for glucose values across all regions was 4%, when the two MRI acquisitions were contrasted. There was no systematic increase or decrease in the metabolic rate values when co-registration and partial volume correction was changed from the 1.5 T to 3 T scans: the mean raw difference in values was 0.3%. Nevertheless, an analysis using only 1.5 T data was also performed to ensure that combining data from different MRI scanners did not artefactually bias results. For the voxel-based morphometry analysis described below, only the scans acquired on the same 1.5 T scanner were used.

Image Analysis FDG-PET

The remaining stages of the image processing and statistical analysis were performed as previously described (Nestor *et al.*, 2003a) using MATLAB (The Mathworks, Natick, MA, USA). Briefly, PET scans were coregistered to each individual's MRI and then spatially normalized to

the T1-MR template in SPM (based on the standard brain of the Montreal Neurological Institute).

Calculation of cerebral metabolic rate for glucose (mmol/min/dl) in regions of interest

Regions of interest were defined on a normalized T1-MRI template for the three surfaces of the prefrontal cortex bilaterally (medial, orbital and dorsolateral), together with the temporal poles and superior parietal cortex (Fig. 1). The location of frontotemporal regions of interest was based on previous FDG-PET studies in frontotemporal dementia using statistical parametric mapping that have highlighted these areas as being severely hypometabolic (Garraux *et al.*, 1999; Salmon *et al.*, 2003; Diehl *et al.*, 2004; Nestor *et al.*, 2006). The subjects' PET scans were coregistered to their MRI and then spatially normalized to the T1-template in statistical parametric mapping. The 3D region of interest object map was then overlaid, and the cerebral metabolic rate for glucose calculated for each region of interest using the autoradiographic method. As the aim of the region of interest study was absolute metabolic rate quantification, a three compartment partial volume correction was applied to each region to correct for artefactual decline in metabolic rate values due to regional atrophy (Meltzer *et al.*, 1999). This method uses the spatially normalized grey matter and white matter segments from the MRI, smoothed to the resolution of the cerebral metabolic rate for glucose map. Within each region it is assumed that the metabolic rate for grey and white matter is homogeneous and the rate for other segments (cerebrospinal fluid, skull and scalp) is zero. Mean regional metabolic rate values for grey and white matter are determined from the voxel cerebral metabolic rate for glucose values within the region plotted as a function of grey matter/(grey matter + white matter). Within the confines of the assumptions made, this method corrects for the variable artefactual hypometabolism due to partial volume error from cerebrospinal fluid and also determines partial volume corrected grey and white matter metabolic values. The regional metabolic values quoted from now on are the volume-weighted mean of the grey and white matter values.

From the 10 regional cerebral metabolic rate for glucose ratings, two indices were calculated: a mean frontotemporal cerebral metabolic rate for glucose, which was the average of the eight values from the

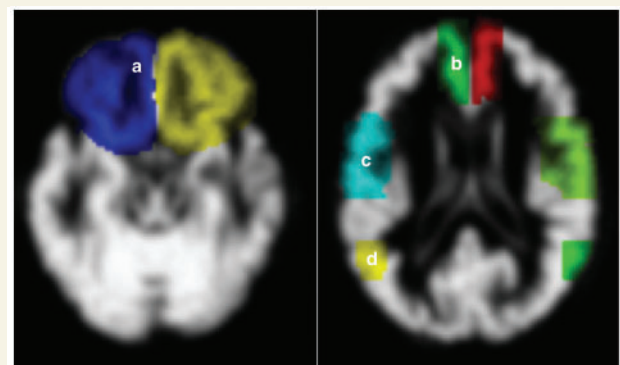


Figure 1 Representative axial images through three-dimensional regions of interest (a) orbitofrontal cortex, (b) medial prefrontal cortex, (c) dorsolateral prefrontal cortex and (d) parietal cortex; anterior temporal lobe cortex region of interest not shown.

frontal and temporal lobes, and a control parietal region calculated as the average of the two parietal lobe values.

MRI Scan rating

Subjects with clinically diagnosed behavioural variant frontotemporal dementia were divided into two groups based on structural imaging features. MRI scans for both subjects and controls were rated for frontal and anterior temporal atrophy using a recently validated visual rating scale (Davies *et al.*, 2006; Kipps *et al.*, 2007a). A single coronal slice, through the temporal pole immediately anterior to the slice where the 'temporal stem' connects frontal and temporal lobes is used and the scale ranges from 0 (normal) to 4 (severe atrophy). In previous work, controls were uniformly rated as 0 or 1, and this was taken to be the normal range (Kipps *et al.*, 2007a). Ratings between 2 and 4 were regarded as abnormal.

All images for both subjects and controls were anonymized, placed in random order, and rated three times by the same rater (CK), blind to any identifying features or clinical history. Intra-rater agreement was excellent ($\kappa=0.94$) for the first two ratings, and discrepancies were resolved by the use of the third rating where necessary. This is in keeping with previous work which showed inter-rater agreement $\kappa=0.62-0.71$ and intra-rater $\kappa=0.79-0.83$ across a wider cohort of frontotemporal dementia patients (Kipps *et al.*, 2007a). The subject group was divided into two: those in whom the MRI scan was rated in the control range (all regional ratings 0–1; MRI-normal, $n=9$), those in whom the scan was rated abnormal (any regional rating 2–4; MRI-abnormal, $n=15$). In total, five patients from this study (three MRI-abnormal and two MRI-normal) were part of an earlier study where MRI, but not PET changes were reported (Davies *et al.*, 2006).

Clinical data

At the time of scanning, all participants undertook the Addenbrooke's Cognitive Examination (ACE) (Mathuranath *et al.*, 2000) and the Mini-Mental Status Examination (MMSE) (Folstein *et al.*, 1975); most patients had these repeated annually from their first presentation. Additionally, all FTD patients were assessed annually on the Clinical Dementia Rating score (CDR) (Morris, 1997), and the Cambridge Behavioural Inventory (CBI), an 81-item caregiver rating of neuropsychiatric symptoms, well validated in dementia (Bozeat *et al.*, 2000) with good concurrent validity with the NPI (Cummings *et al.*, 1994; Nagahama *et al.*, 2006).

Statistical Analysis

Demographic and clinical data were analysed with unpaired *t*-tests or one-way ANOVA (CBI, CDR—sum of boxes, duration from symptom onset to PET scanning) or chi-square tests (gender) as appropriate. Where preliminary analysis suggested that the data were not normally distributed, non-parametric tests were used (Mann—Whitney U: MMSE, ACE and CDR).

The imaging data were first analysed in a repeated measures ANOVA, three group (MRI-normal, MRI-abnormal and Controls) \times 2 regions (mean frontotemporal and parietal cerebral metabolic rates for glucose). Main effects and the interaction were modelled with subsequent planned *post hoc* univariate ANOVAs comparing groups. A subsequent series of univariate ANOVAs modelled group differences across the 10 individual regions of interest in the frontal, temporal and parietal regions; pre-specified *post hoc* contrasts were corrected using the 'Bonferroni method'.

Voxel-based morphometry analysis

To check that the visual rating of individual MRI scans was not insensitive to subtle abnormalities that might be evident in averaged data, a voxel-based morphometry analysis was undertaken. Individual MRI images ($n=14$ MRI-abnormal, $n=8$ MRI-normal and $n=8$ controls) that had all been performed on the same 1.5T MRI scanner were further analysed using the technique of voxel-based morphometry in SPM5 (Wellcome Department of Cognitive Neurology, UK). The pre-processed scans were modulated to allow grey matter volume inferences and smoothed using an 8mm FWHM smoothing kernel. An ANCOVA design matrix was used to test for regions of grey matter volume contraction between the three groups (MRI-normal, MRI-abnormal and controls), with total grey matter included as a covariate in the model. Voxel values in frontal, anterior temporal and cerebellar vermis regions were extracted from the images using MarsBaR (Brett *et al.*, 2002) (marsbar.sourceforge.net) and exported to SPSS (SPSS 14.0, SPSS Inc, Chicago, IL, USA). To assess the validity of the visual rating scale, the extracted voxel values were correlated (Spearman's rho) with the MRI rating scale scores obtained using the visual rating scale. Regional grey matter volume in the frontal, anterior temporal and cerebellar regions was then compared between MRI groups (MRI-normal versus MRI-abnormal).

Results

Demographic data

There was no significant difference in age between patient and control groups [$F(2,33)=0.79$, $P>0.05$], and importantly, the duration of illness at final follow-up (both from symptom onset and from presentation) was similar in the two frontotemporal dementia subgroups, as was the duration of illness at the time of PET scanning (all $P>0.05$, see Table 1). All patients had follow-up data available including post-mortem data in six (see below) although for one MRI-abnormal patient, ACE was only available at presentation. There was only one woman in the MRI-normal group, but the gender ratio was not significantly different from that of controls or the MRI-abnormal group ($\chi^2=3.9$, $df=2$, $P>0.05$). As none of these potential confounders were significantly different between the two groups, they were not included as covariates in subsequent analyses.

Imaging

Mean Regional Metabolic Rate (Frontotemporal versus Parietal)

A repeated measures ANOVA showed a main effect of region, [$F(1,33)=149.6$, $P<0.0001$], in that frontotemporal regions had a significantly lower metabolic rate than parietal regions, but no main effect of group [$F(2,33)=3.1$, $P=0.06$] (Fig. 2a). Importantly, however, there was a region \times group interaction [$F(2,33)=10.0$, $P<0.001$]. Planned *post hoc* univariate ANOVAs showed the source of this interaction was due to significantly lower frontotemporal, but not parietal, hypometabolism in the MRI-abnormal group compared with controls (mean frontotemporal difference: $P<0.01$).

Table 1 Demographic characteristics

	Clinical FTD (n=24)	MRI-normal (n=9)	MRI-abnormal (n=15)	Controls (n=12)
Age	59.8 (7.1)	59.9 (9.4)	59.8 (5.9)	58.9 (4.4)
Gender	16M:8F	8M:1F	8M:7F	6M:6F
Duration to final follow-up (years from stated onset)	6.4 (3.1)	6.0 (2.7)	6.6 (3.4)	–
Duration to final follow-up (years from presentation)	4.0 (3.2)	4.3 (2.4)	3.8 (3.6)	–
Duration at time of PET scan (years from presentation)	1.8 (2.9)	1.7 (1.8)	1.9 (3.5)	–
MMSE	26.0 (2.9)	28.1 (1.1) [†]	24.7 (3.1) ^{†,*}	29.7 (0.5)
ACE at scan	74.2 (15.5)	87.2 (5.4) [†]	66.3 (14.3) ^{†,*}	96.3 (2.8)
ACE at presentation	78.5 (15.2)	89.9 (4.5) [†]	71.7 (15.3) ^{†,*}	96.3 (2.8)
ACE at last review	62.7 (27.1)	89.0 (6.7)	47.7 (22.3) ^{†,*}	93.8 (4.4)
CDR	0.9 (0.6)	1.1 (0.8)	0.9 (0.5)	–
CDR—sum of boxes	5.4 (3.5)	6.3 (4.1)	5.2 (3.1)	–
NPI	38.2 (20.7)	47.0 (18.2)	34.3 (21.7)	–
CBI	91.0 (38.2)	104.8 (38.6)	86.3 (36.1)	–

Values are given as Mean (SD).

[†]Significantly worse than controls ($P < 0.01$).

*Significantly worse than MRI-normal group ($P < 0.01$).

Clinical behavioural variant frontotemporal dementia category represents the combined group, diagnosed without reference to imaging. On NPI and CBI, higher scores indicate greater endorsement of behavioural disturbance by carers. For NPI, three frontotemporal dementia patients not assessed. Ratings at presentation unless otherwise stated. Duration measured to last contact or death.

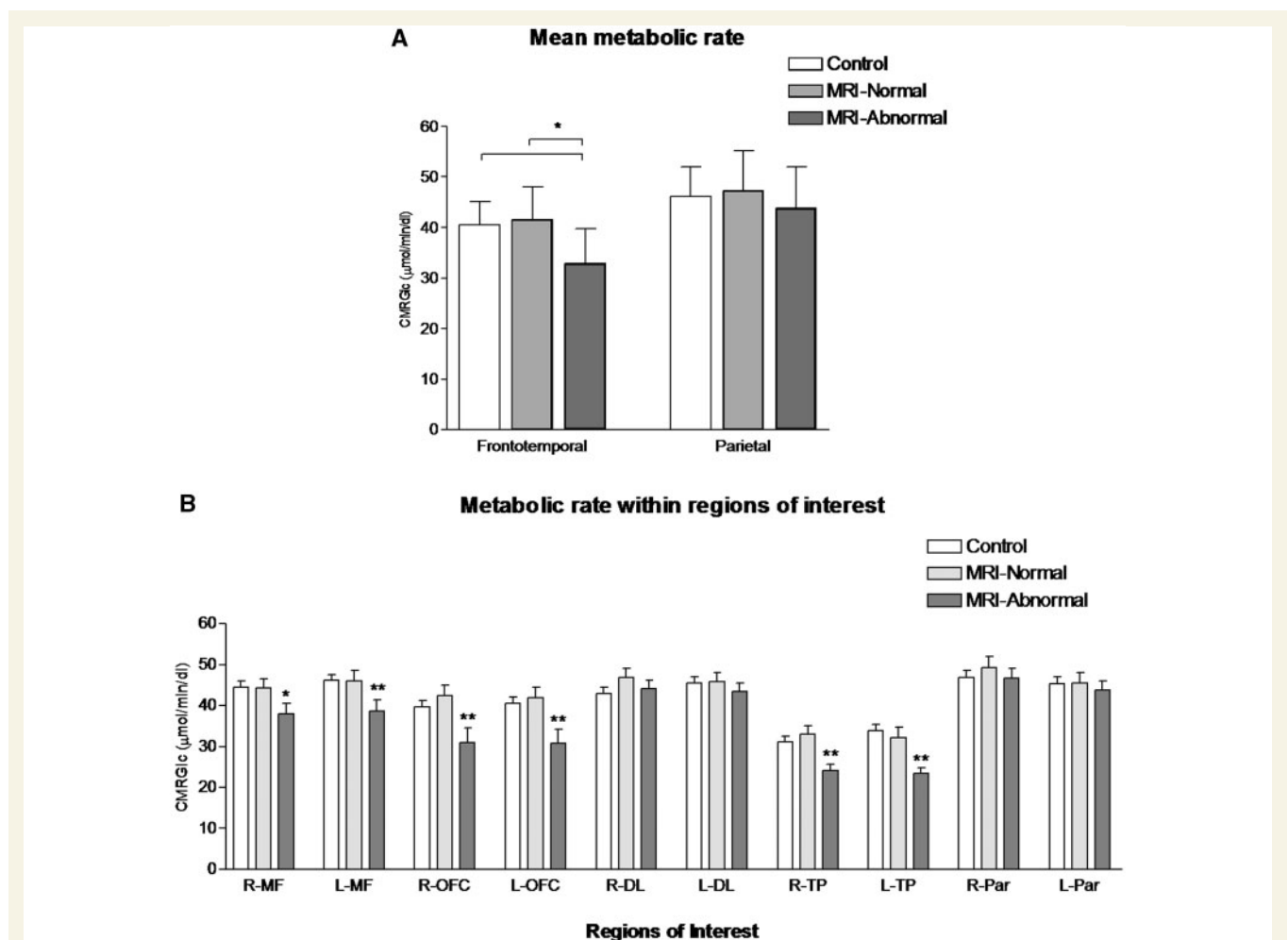


Figure 2 (A) Comparison of average metabolic rate in frontotemporal and parietal regions. (B) Metabolic rates across regions MRI-normal, -abnormal and control groups. *Indicates MRI-abnormal group significantly lower cerebral metabolic rate for glucose ($\mu\text{mol}/\text{min}/\text{dl}$) compared with MRI-normal group ($P < 0.05$), **indicates significantly lower cerebral metabolic rate for glucose ($\mu\text{mol}/\text{min}/\text{dl}$) in MRI-abnormal group compared with both controls and MRI-normal group ($P < 0.05$). R, L (Right, Left) MF = medial frontal, OFC = orbitofrontal, DL = dorsolateral, TP = temporal pole, Par = Parietal.

and the MRI-normal group (mean frontotemporal difference: $P < 0.01$).

In contrast, there were no significant differences between controls and MRI-normal subjects in any region (all $P > 0.05$). Correlation analysis showed that there was no relationship between duration of symptoms at time of PET scanning and frontotemporal cerebral metabolic rate for glucose values (Pearson's $r = 0.05$) in the clinical frontotemporal dementia group as a whole.

Regional Metabolic Rates in Regions of Interest

Univariate ANOVAs comparing the metabolic rate between groups were performed in each of the 10 ROIs (Fig. 2b). There were significant differences between groups in the medial prefrontal, orbitofrontal and temporal polar, but not dorsolateral prefrontal or parietal regions [medial prefrontal—(R): $F(2,33) = 5.3$, $P < 0.05$; (L): $F(2,33) = 6.7$, $P < 0.01$; orbitofrontal—(R): $F(2,33) = 9.3$, $P < 0.01$; (L): $F(2,33) = 9.3$, $P < 0.01$; temporal poles—(R): $F(2,33) = 7.6$, $P < 0.01$; (L): $F(2,33) = 17.2$, $P < 0.001$;

dorsolateral prefrontal—(R): $F(2,33) = 0.7$, $P > 0.1$; (L): $F(2,33) = 1.3$, $P > 0.1$; parietal—(R): $F(2,33) = 0.69$, $P > 0.1$; (L): $F(2,33) = 0.6$, $P > 0.1$]. Planned *post hoc* contrasts (all *Bonferroni* corrected) showed that metabolic rates were not significantly different between controls and the MRI-normal group in any of the three frontal or two parietal regions. The MRI-abnormal group, by contrast, had significantly reduced metabolism compared to both controls and the MRI-normal groups in the medial prefrontal, orbitofrontal and temporal polar cortices (all $P < 0.05$), but not dorsolateral prefrontal or parietal regions bilaterally. Illustrative examples of axial, coronal and sagittal coregistered FDG-PET images from a control, a MRI-abnormal and a MRI-normal subject are shown in Fig. 3.

The analyses were repeated with a total of 27 subjects who had a 1.5T scan on the same scanner (Controls=8, MRI-normal=9 and MRI-abnormal=10). In a repeated measures design, there was a main effect of region [$F(1,24) = 134.2$, $P < 0.001$] highlighting a general reduction in frontal compared with parietal metabolic rate (both normalized to cerebellar cerebral metabolic rate

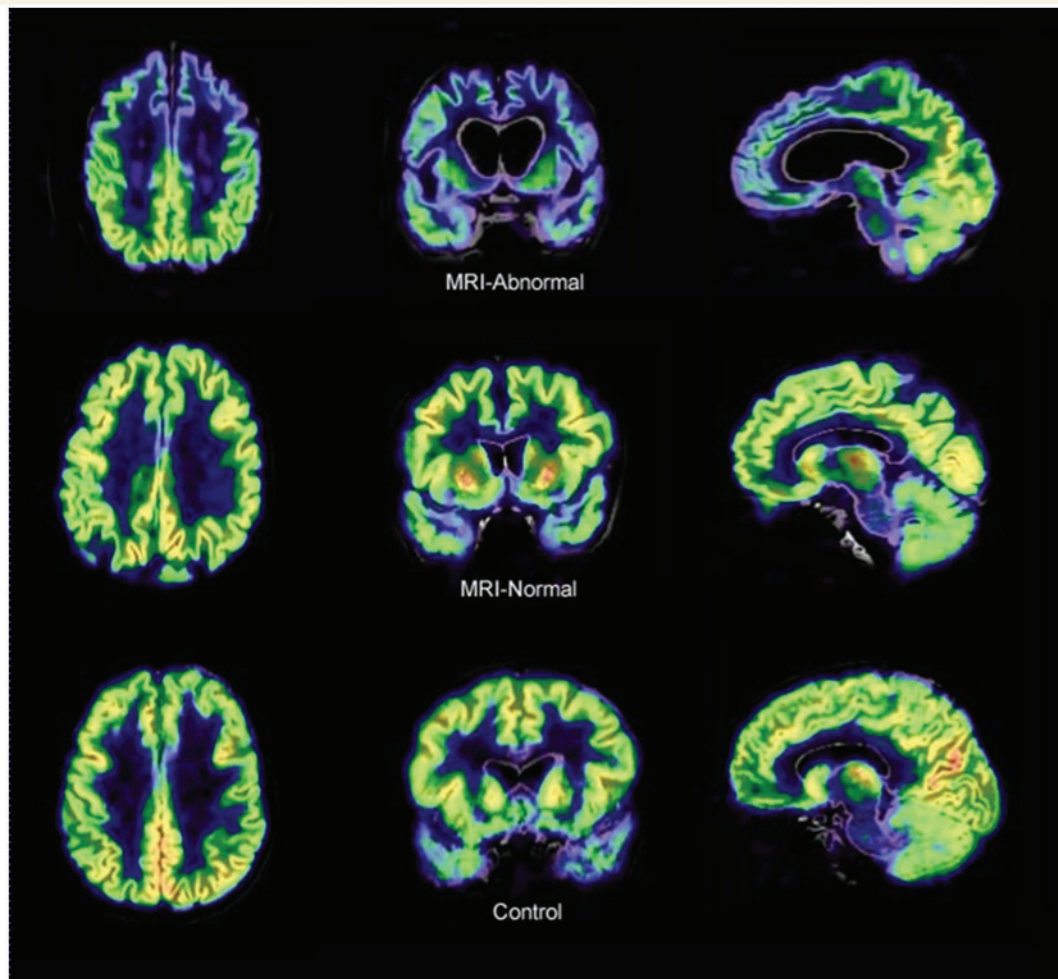


Figure 3 Coregistered MRI and PET images for representative behavioural variant frontotemporal dementia (MRI-Abnormal), behavioural variant frontotemporal dementia-phenocopy (MRI-Normal) and control subjects. Images are scaled according to colour bar on left, and show clear frontotemporal hypometabolism in behavioural variant frontotemporal dementia relative to both the phenocopy and controls which do not differ from each other.

for glucose). There was also an effect of group [$F(1,24)=5.17$, $P<0.05$]; controls had preserved metabolism as did the MRI-normal group, however the MRI-abnormal group did not. Importantly, there was a region \times group interaction [$F(2,24)=6.66$, $P<0.01$]. *Post hoc* contrasts and examination of interaction graphs showed that this was because the behavioural variant frontotemporal dementia cases with an abnormal MRI had disproportionate impairment of frontotemporal metabolism compared to both controls ($P<0.01$) and the behavioural variant frontotemporal dementia patients with a normal scan ($P<0.05$), confirming the earlier result with a mixture of 3 T and 1.5 T scans.

Structural image analysis and comparison with Visual Rating Scale

There was marked frontotemporal volume loss in the MRI-abnormal group relative to the MRI-normal subjects (see supplementary information for exact coordinates). In particular, this involved the medial prefrontal, orbitofrontal and insula regions but largely spared the dorsolateral prefrontal cortex (Fig. 4). There was also significant volume loss in the anterior temporal lobes, but parietal, occipital and cerebellar regions were spared. Most importantly, however, the frontotemporal dementia subjects rated as having scans within the normal range on the analogue scale (MRI-normal, ratings 0–1) had no volume loss relative to control subjects even at substantially relaxed statistical thresholds.

The scores on the visual rating scale were then rank correlated (Spearman's rho) with voxel values extracted from the frontal lobe, anterior temporal region and cerebellar vermis. There was a strong correlation between both frontal and temporal lobe scores across the two methods (Table 2). The cerebellum (vermis), included as a control region did not show a significant correlation. An ANOVA comparing regional ratings across the combined overall groups defined by the visual rating scale (MRI-abnormal versus MRI-normal plus controls) showed significant reductions in the volume of all frontotemporal regions but not the cerebellum (Fig. 5).

Clinical and behavioural data

At the time of presentation, the two patient groups differed from each other and from controls on the ACE (Kruskal–Wallis $\chi^2=21.64$, $df=2$, $P<0.001$; *post hoc* Mann–Whitney U: MRI-abnormal < MRI-normal < Controls, $P<0.01$), but there was significant overlap of individual ACE scores in the MRI-normal and MRI-abnormal frontotemporal dementia subgroups (Fig. 6). At the time of last follow-up, there remained a significant overall difference between groups, but the MRI-normal group performed at a level equivalent to controls, and better than the MRI-abnormal group (Kruskal–Wallis $\chi^2=22.47$, $df=2$, $P<0.001$;

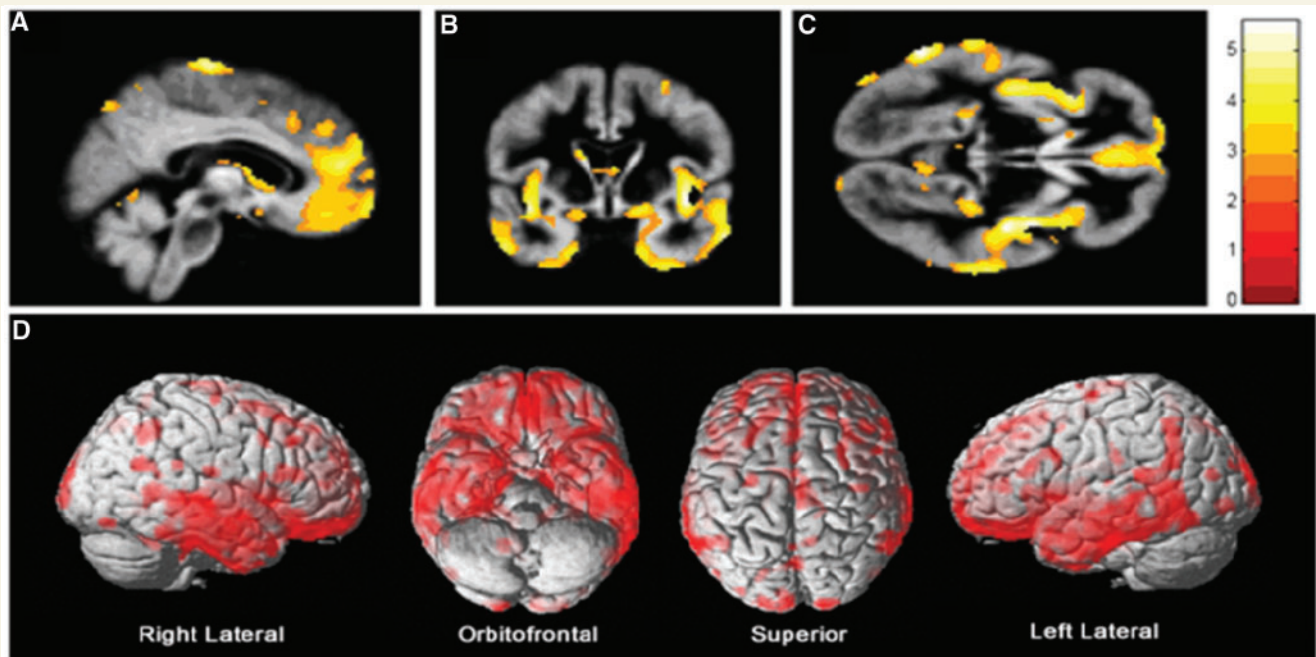


Figure 4 Statistical parametric map of grey matter loss in MRI-Abnormal frontotemporal dementia relative to MRI-Normal subjects (contrast $-1\ 1$) rendered on mean image of grey matter segment in controls (a–c at MNI co-ordinates $x=-4$, $y=-2$, $z=-5$), and surface rendered on single subject brain (d). The image is thresholded at false discovery rate $P<0.05$ (cluster threshold >10). The colour bar to the right of the image shows the significance thresholds (t-scores). Note the marked frontotemporal grey matter volume contraction, particularly medial prefrontal, orbital and insula, in the MRI-abnormal behavioural variant frontotemporal dementia patients relative to the clinically similar MRI-normal cohort. There was relative sparing of the dorsolateral prefrontal cortex and minimal involvement of parietal areas and the cerebellum. A very similar pattern of atrophy is seen in the MRI-abnormal group relative to controls (not shown). In contrast, the MRI-normal group had no grey matter volume loss relative to controls even at relaxed statistical thresholds.

Table 2 Visual Rating Scale and regional statistical parametric mapping voxel value correlation

		Visual Rating Scale				
		L Frontal	R Frontal	L Ant Temp	R Ant Temp	Overall Rating
Voxel	L Frontal	−0.52*	−0.50*	−0.11	0.11	−0.51*
Values	R Frontal	−0.54**	−0.59**	0.01	0.07	−0.52*
(SPM)	L Ant Temp	−0.62**	−0.42	−0.73***	−0.47*	−0.66**
	R Ant Temp	−0.54**	−0.39	−0.65**	−0.64**	−0.58**
	Cerebellum	−0.40	−0.38	−0.11	0.05	−0.36

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

L=Left; R=Right; Ant Temp=Anterior Temporal Lobe; Frontal=Frontal Lobe; Cerebellum=Cerebellar Vermis.

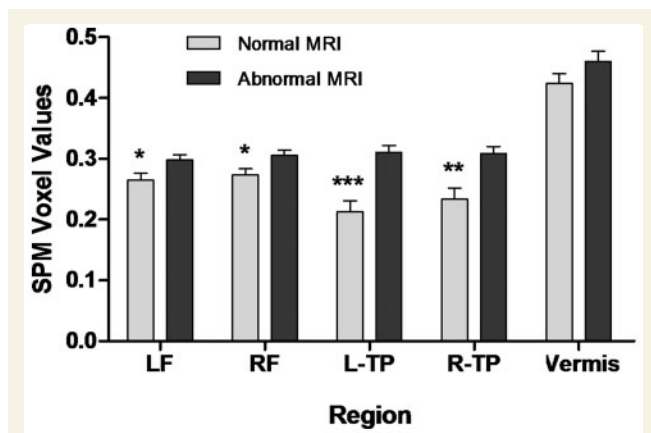


Figure 5 Mean (+SEM) in frontal, anterior temporal and cerebellar regions using voxel values from SPM analysis grouped by Visual Rating Scale regions (behavioural variant frontotemporal dementia subjects only: MRI-normal versus MRI-abnormal). There are significant volume reductions in frontal (bilateral, $P < 0.05$) and anterior temporal (left $P < 0.001$, right $P < 0.01$) regions but not the cerebellum.

post hoc Mann–Whitney U: MRI abnormal < MRI-normal = Control, $P < 0.001$).

There were non-significantly increased endorsements on the CBI, NPI and the CDR-sum of boxes in the MRI-normal group compared with the MRI-abnormal group at presentation (Table 1). Total score on the CBI correlated strongly with total score on the NPI (Spearman's rho 0.88, $P < 0.0001$) across the patient cohort. The NPI profile of symptoms characteristic of FTD was virtually identical across the two groups (Fig. 6).

Most patients underwent an extensive neuropsychological battery at clinical presentation including tests of working memory (digit span), verbal memory (Rey Auditory Verbal Learning Test), non-verbal memory (Rey-Osterreith Complex Figure), semantic memory (Graded Naming Test) and executive functions (Letter Fluency, Trailmaking Test, Hayling and Brixton Spatial Anticipation Tests and Wisconsin Card sorting Test); see Table 3. There were significant intragroup differences for letter fluency, the Hayling test and the Graded Naming test with post hoc comparisons showing poorer performance in the MRI-abnormal group compared to controls but no significant difference between the frontotemporal dementia subgroups.

Case-by-case concordance of MRI and PET imaging

Frontal and temporal regions (bilaterally) were individually compared against control values. A PET scan was designated as being abnormal where cerebral metabolic rate for glucose in at least one of the four regions was 2 SD less than the control mean for that region (Table 4).

In the MRI-normal group, 2/9 patients had an abnormal PET scan. One of these (male with symptom onset at age 70 years; age 77 years at most recent review) had significant frontal and parietal hypometabolism. Although personality changes suggestive of behavioural variant frontotemporal dementia were prominent early features, disorientation and memory problems more typical of probable Alzheimer's disease emerged over time. The second (male, symptom onset at 60 years; age 67 years at most recent review) remains stable and cognitively intact. This patient had a complex past medical history including cyclophosphamide treatment for polyarteritis nodosa secondary to hepatitis B infection.

When the MRI scan was rated as being abnormal, only one of the 15 patients had normal PET regional ratings. This individual remains clinically unchanged 5 years from symptom onset; interestingly his MRI was a rather borderline scan which was rated abnormally (2/4, the mildest abnormal rating) in only one of the four frontotemporal regions.

The negative predictive value for a normal MRI scan in predicting a normal PET scan in this study was 87.5%.

Pathological confirmation

Eight of the MRI-abnormal group have since died, of whom six underwent necropsy. All had confirmed frontotemporal dementia (three tau positive pathology, three ubiquitin positive pathology). The MRI-normal group are all still living.

Discussion

Several important findings emerged from this study. The absence of brain atrophy in behavioural variant frontotemporal dementia using a simple visual analogue rating scale for structural imaging (MRI) was predictive of normal metabolism in frontotemporal regions, irrespective of disease duration. This suggests a lack of neurodegeneration in these individuals, and strengthens the case for the existence of a non-neurodegenerative phenocopy of the disease. In cases characterized by definite brain atrophy there was

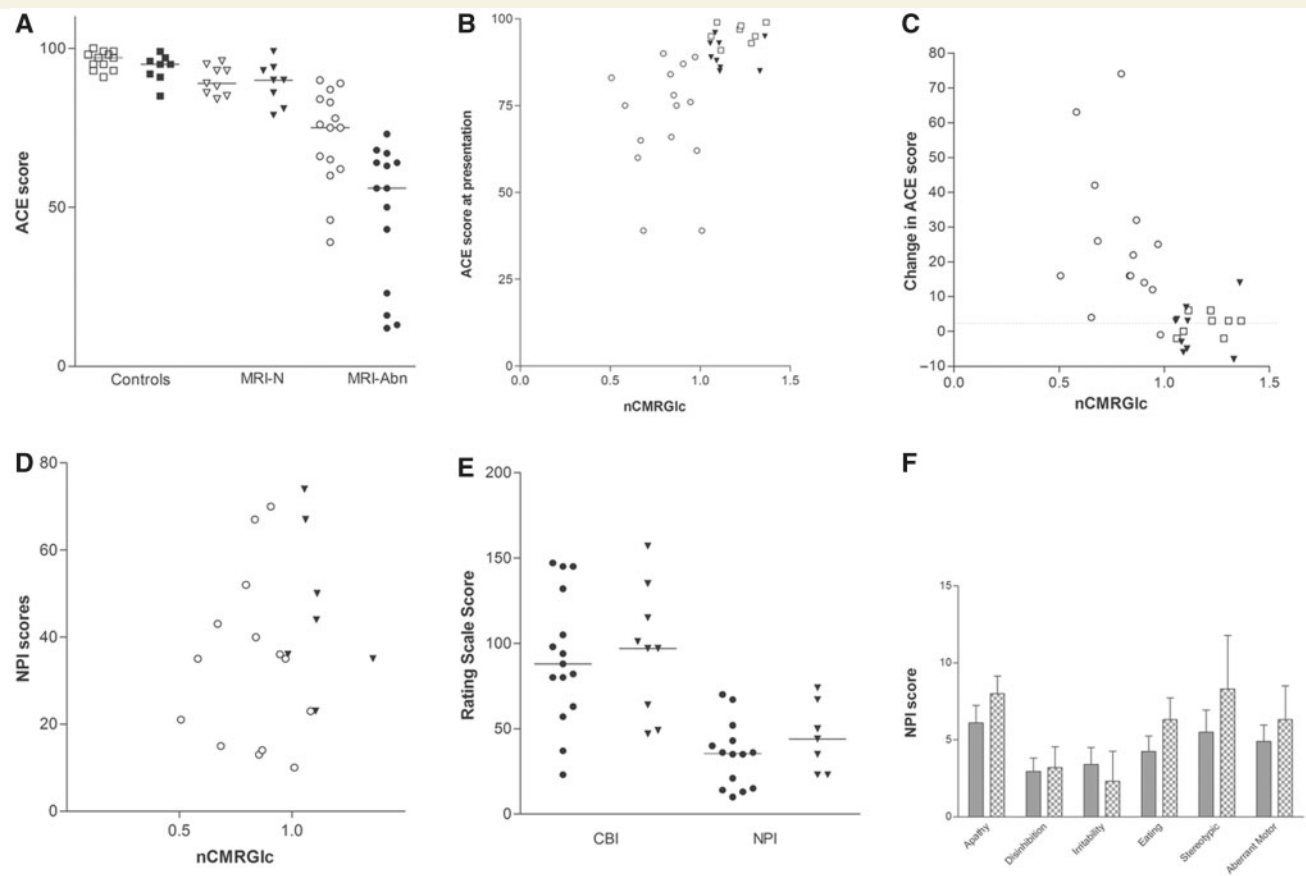


Figure 6 Cognitive and behavioural profiles and relationship to metabolic rate. Cognitive (A–C): (A) Individual patient and scores (controls—squares, MRI-normal bvftd subgroup—triangles, MRI-abnormal subgroup—circles, horizontal line represents median for groups) on ACE from time of presentation (open symbols) to last available follow-up (closed symbols); (B) Relationship of ACE score to frontotemporal metabolic rate across groups normalized to individual cerebellar values (nCMRglc). (C) Relationship of change in ACE score to frontotemporal metabolism across groups. Mean frontotemporal metabolic rate indicated by dashed line; Behavioural (D–F): (D) Individual scores on CBI and NPI for behavioural variant frontotemporal dementia subgroups (circles: MRI-abnormal; triangles: MRI-normal group). Median scores indicated by horizontal line for each subgroup; (E) Relationship of NPI score to frontotemporal metabolic rate across subgroups; (F) Profile of NPI domain subscores for MRI-abnormal (shaded) and MRI-normal groups (stippled).

regional metabolic and structural heterogeneity, with temporal, orbitofrontal and medial prefrontal regions most affected; this may explain key aspects of the clinical presentation, and the relative lack of 'consistent' impairment on commonly used cognitive screening instruments. Patients with structural abnormalities deteriorated cognitively relative to their imaging-normal counterparts, and of these, all who have died have been shown to have pathology consistent with frontotemporal lobe degeneration. We were also able to validate a semi-quantitative visual rating scale of atrophy against an automated method (voxel-based morphometry) and to confirm concordance between structural and metabolic changes.

We were careful to quantify the metabolic rate in several brain regions believed to be critical for the genesis of the behavioural syndrome and in particular where previous studies suggest the earliest pathology is to be found in behavioural variant frontotemporal dementia (Krill *et al.*, 2005). Yet, despite this, the group without MRI changes had normal metabolic rates in frontotemporal regions. The duration of illness was similar in the two subgroups,

which argues strongly against the suggestion that imaging-normal behavioural variant frontotemporal dementia patients are simply at an earlier stage of disease, when atrophy is insufficiently established. This is supported by the absence of a significant correlation between symptom duration at the time of PET scanning, and frontotemporal cerebral metabolic rate for glucose values in the clinical frontotemporal dementia group as a whole.

FDG-PET is regarded as a highly sensitive marker of neuronal dysfunction (Minoshima *et al.*, 1997; Masdeu *et al.*, 2005), and many studies, including those with presymptomatic individuals with neurodegenerative disease describe metabolic deficits using this imaging modality (Nestor *et al.*, 2004; Eckert *et al.*, 2005; Inagaki *et al.*, 2005; Ciarmiello *et al.*, 2006; Cortelli *et al.*, 2006). The absence of hypometabolism in our cases suggests that at least some of these patients may not have a neurodegenerative syndrome. Whilst it could be argued that the visual rating scale we used is insensitive to subtle pathology, there was good correlation between regional ratings on this scale and regional voxel values extracted from the SPM analysis. Furthermore, there was no

Table 3 Neuropsychology test profile of FTD subgroups and controls

Test	MRI-abnormal		MRI-Normal		Control		Post hoc
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
Digit span							
Forwards	14	6.4 (1.0)	7	6.3 (1.4)	–	–	NS
Backwards	14	4.2 (1.4)	7	4.4 (1.4)	–	–	NS
RAVLT							
A6	9	6.8 (2.9)	9	6.3 (2.6)	10	9.5 (3.2)	NS
A30	10	5.5 (4.4)	9	5.4 (3.6)	10	10.2 (3.1)	MRI-n = MRI-abn < Co, <i>P</i> < 0.05
Recognition	10	12.2 (2.7)	9	12.1 (2.8)	10	14.1 (1.1)	NS
Rey-CF							
Copy	18	32.9 (5.1)	9	33.9 (2.1)	10	34.2 (2.3)	NS
Delayed	15	12.7 (8.0)	7	13.4 (6.7)	9	16.9 (4.0)	NS
GNT							
Words	15	12.9 (9.6)	9	20.8 (5.3)	10	22.6 (4.9)	MRI-abn < Co, <i>P</i> = 0.01
Letter fluency							
FAS	14	22.6 (17.0)	7	32.4 (13.9)	10	38.2 (12.8)	MRI-abn < Co, <i>P</i> = 0.06
Trails							
A	9	61.2 (33.8)	7	51.6 (17.3)	10	38.0 (8.3)	NS
B	8	159.0 (145.6)	8	112.9 (37.2)	10	90.0 (28.4)	NS
Hayling							
Scaled score	12	2.2 (1.9)	6	4.2 (1.9)	10	5.3 (1.3)	MRI-abn < Co, <i>P</i> < 0.001; MRI-n = MRI-abn; MRI-n = Co
Brixton							
Scaled score	8	5.6 (2.0)	9	4.7 (2.6)	10	5.7 (1.2)	NS
WCST							
Categories	12	4.6 (2.2)	8	4.1 (1.9)	–	–	NS

RAVLT = Rey Auditory Verbal Learning Test; A6 = Word List Recall after interference list presented; A7 = Delayed Word List Recall at 30 min; GNT = Graded Naming Test; FAS = combined score for verbal letter fluency using letters f, a, s; Trails A and B = Trailmaking Test Parts A and B; WCST = Wisconsin Cardsorting Test; MRI-N = frontotemporal dementia subgroup with normal imaging; MRI-Abn = frontotemporal dementia subgroup with abnormal imaging; Co = controls; NS = no significant difference between groups; *n* = number of subjects performing test.

Table 4 MRI and PET concordance

	Normal PET		Abnormal PET		Total
	Progressors	Non-progressors	Progressors	Non-progressors	
Normal MRI	–	7	1	1	9
Abnormal MRI	–	1	14	–	15

MRI was rated as abnormal if any of four frontotemporal regions (L, R— anterior temporal, frontal) was rated as two or above on the visual rating scale. A PET scan was designated as being abnormal when cerebral metabolic rate for glucose in at least one of the four regions was 2 SD less than the control mean for that region Progressors = patients who had clinical progression after presentation; Non-progressors = patients who appeared clinically stable after presentation despite a clear indication from carers that there had been a distinct change and deterioration in previous functioning from time of symptom onset to presentation. See text for details of cases where MRI and PET were discordant.

volume loss seen in the frontotemporal dementia MRI-normal group relative to controls even at very relaxed statistical thresholds. The marked frontotemporal atrophy in the MRI-abnormal group relative to both controls and the frontotemporal dementia patients with a normal MRI provides strong support for the validity of the scale.

Cognitive function was not entirely normal in our imaging-normal behavioural variant frontotemporal dementia group. Their mean score on the ACE fell midway between the scores for maximum sensitivity (82) and specificity (88) for neurodegenerative disease (Mathuranath *et al.*, 2000), even though

group performance was not significantly worse than controls at their last review. Importantly, all but one remained stable over time from a cognitive perspective. Interestingly, the only decliner had significant frontal *and* parietal hypometabolism on PET and has developed a cognitive syndrome typical of clinical Alzheimer's disease. As a group, behavioural variant frontotemporal dementia patients with an abnormal MRI performed worse than both other groups on the ACE, but almost a third had ACE scores that overlapped with the range of the imaging-normal group. This finding has recently been reported in detail elsewhere (Kipps *et al.*, 2008). Their neuropsychological test profiles were

very similar at clinical presentation, but the MRI-abnormal group showed clear deterioration over time. For both frontotemporal dementia groups, behavioural scores remained abnormal, and indistinguishable, throughout the period of clinical observation.

These findings pose a challenging problem for clinical diagnosis. It was recently reported that two patients with ubiquitin-positive pathological changes at post-mortem had minimal atrophy, but these patients progressed to death over 4 and 11 years respectively, unlike our patients (Josephs *et al.*, 2006). In the absence of pathology, we are unable to absolutely exclude a degenerative process but this seems unlikely in view of the lack of progression in such cases sometimes over a decade of follow-up. In support of this supposition, Kertesz *et al.*, 2005 reported a patient, within a larger series with florid behavioural changes who died prematurely and despite extensive neuropathological examination, no evidence of a neurodegenerative disease was found. In addition, a patient diagnosed strictly in accordance with frontotemporal dementia criteria, but excluded from a longitudinal cohort imaged serially using FDG-PET, was found to have no pathology at post-mortem when he later died unexpectedly (Diehl-Schmid *et al.*, 2007).

If these patients do not have neurodegeneration, what alternative explanations are tenable? One possibility is that we have identified a group of patients with marked age-related personality change. It remains controversial, however, as to whether personality traits vary between early adulthood and old-age (Ravenna *et al.*, 2002; Jones *et al.*, 2003; Terracciano *et al.*, 2006). In general, measures of adherence to social norms (self-control, the desire to create a good impression, reduced flexibility) show increases over time, in contrast to social vitality or extraversion (social presence, empathy and self-acceptance), which has a tendency to decline. Several longitudinal studies suggest that these long-term group trends may mask significant individual variability (Ravenna *et al.*, 2002; Jones *et al.*, 2003). The changes in our patients are maladaptive, and indistinguishable from patients with evidence of neurodegeneration. While it remains possible that the behavioural changes we describe here are simply one extreme of normal age-related personality evolution, this seems unlikely.

A number of psychiatric syndromes also warrant consideration. Late onset schizophrenia, or paraphrenia, has a female predominance (unlike our cohort), with hallucinations and persecutory delusions manifesting more commonly, and a lower propensity to formal thought disorder or emotional blunting than in earlier onset schizophrenic presentations (Howard *et al.*, 2000; Sato *et al.*, 2004). Our patients do not, therefore, conform to current concepts of paraphrenia. Hallucinations or delusions suggestive of a psychotic disorder were absent. Depressive symptoms were excluded by formal psychiatric interview in these patients, and were not felt to be an adequate explanation for their symptoms. Several patients had behaviours reminiscent of mania but the clinical features were never sufficient for formal psychiatric diagnosis. Moreover it did not appear to be cyclical and occurred in the absence of a history of long-term mood disorders. There are occasional references in the psychiatric literature to 'chronic mania' (Malhi *et al.*, 2001; Mendhekar *et al.*, 2004); seen more commonly in the pre-antipsychotic era (Kraepelin, 1921), this entity remains indistinct in current practice. A *form fruste* of low-grade

chronic late-onset mania cannot be entirely discounted as a diagnosis in at least some of the patients with normal brain imaging.

Finally, the clinical features of frontotemporal dementia are remarkably similar to many of those seen in the autism-spectrum disorders (ICD-10, 1992; DSM-IV-TR, 2000). Yet, the absence of these features during earlier life, and the insistence by carers that these patients have undergone a distinct change in personality, make such an account implausible. To our knowledge there is no literature that describes the emergence of autism-spectrum disorders in middle age. It is also possible that rather minor personality changes have been exaggerated by some caregivers having received a possible diagnosis of frontotemporal dementia early in their course. Since insight is frequently impaired in behavioural variant frontotemporal dementia, a reliable informant is crucial for the diagnosis. Several studies attest to the dependability of spousal or close relative assessment (Siegler *et al.*, 1994; Strauss and Pasupathi, 1994). Whilst this may not always be an entirely safe assumption, it is difficult, in practice, to know exactly what level of corroboration is sufficient for diagnosis. Most of our cohort was reviewed on a regular basis for several years, and spousal reports of their behaviour remained consistent. Importantly all carers insisted that the behavioural changes represented a distinct change from previous functioning.

Our MRI-abnormal group demonstrated disproportionate hypometabolism of the orbitofrontal and medial prefrontal cortices, with involvement of the temporal poles; a similar finding was seen in the statistical parametric mapping analysis of structural images. A number of studies have reported on the metabolic impairments of frontotemporal regions (Salmon *et al.*, 2003; Diehl *et al.*, 2004; Grimmer *et al.*, 2004; McMurtray *et al.*, 2006; Peters *et al.*, 2006; Salmon *et al.*, 2006), but none have quantified the metabolic rate using simultaneous arterial sampling, and few studies have studied differences in regional metabolism within the frontal lobes (Jeong *et al.*, 2005) in behavioural variant frontotemporal dementia. These findings provide additional evidence on the spread of pathology through the brain, and are concordant with previously reported pathological series (Kril and Halliday, 2004; Kril *et al.*, 2005). Although there was marked heterogeneity across subjects, no individual in the MRI-abnormal group showed more hypometabolism of dorsolateral prefrontal cortex than either the orbitofrontal or medial prefrontal region. Similarly, the structural analysis showed relative sparing of the dorsolateral prefrontal cortex. The results may also help explain the relative insensitivity in behavioural variant frontotemporal dementia of neuropsychological test batteries which access executive function performance, that are thought to preferentially engage dorsolateral prefrontal region (Alvarez and Emory, 2006).

The most significant limitation in the present study is the lack of neuropathology in the MRI-normal group. These patients, overwhelmingly men in their 50s and 60s, are likely to live for a considerable time unless they develop other inter-current illnesses. The development of neurotransmitter or pathology-specific ligands may shed light on the pathogenesis but longitudinal follow-up to autopsy is clearly vital. The ratio of progressors to non-progressors should not be taken to reflect their relative prevalence in the community. Those without MRI-abnormalities remain stable and in some cohorts may continue to attend

research-based clinics, whilst those with progressive disease typically develop features of generalized dementia within a few years and discontinue their involvement.

There are several important clinical implications of these findings. The negative predictive value of a normal MRI scan for behavioural variant frontotemporal dementia diagnosis in this study is high (87.5%), assuming that a normal PET scan predicts a lack of neurodegeneration. Thus it may be prudent to withhold diagnosis in patients with 'apparent behavioural variant frontotemporal dementia' in whom there is normal imaging and no apparent change on longitudinal follow-up. It also mandates very careful clinical review and possibly additional corroboration in such cases. Such patients are liable to significantly dilute the power of trials of potential disease-modifying drugs in frontotemporal dementia in view of their lack of progression, and it would be wise to exclude them until more is known about their ultimate diagnosis (Kipps *et al.*, 2008). These observations also raise important questions about the current consensus criteria for frontotemporal dementia in general, and advocate a more prominent role for imaging findings in clinical diagnosis. The results suggest that the addition of imaging criteria (i.e. frontotemporal abnormality on either structural or functional imaging) for diagnosis of frontotemporal dementia may improve specificity, particularly in those with behavioural symptoms who constitute the largest proportion of frontotemporal dementia cases; this is important in early diagnosis where cognitive performance may still be normal in this group. In contrast, those with normal imaging represent a diagnostic conundrum at present. Clearly more work, including most importantly, pathological analysis, is necessary.

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References

- Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev* 2006; 16: 17–42.
- Bozeat S, Gregory CA, Lambon Ralph MA, Hodges JR. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2000; 69: 178–86.
- Brett M, Anton J, Valabregue R, Poline J. Region of interest analysis using an SPM toolbox (abstract). *Neuroimage* 2002; 16: 2.
- Broe M, Hodges JR, Schofield E, Shepherd CE, Kril JJ, Halliday GM. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology* 2003; 60: 1005–11.
- Brun A, Englund B, Gustafson L, Passant U, Mann D, Neary D, *et al.* Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry* 1994; 57: 416–8.
- Ciarmiello A, Cannella M, Latoria S, Simonelli M, Frati L, Rubinsztein DC, *et al.* Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. *J Nucl Med* 2006; 47: 215–22.
- Cortelli P, Perani D, Montagna P, Gallassi R, Tinuper P, Federica P, *et al.* Pre-symptomatic diagnosis in fatal familial insomnia: serial neurophysiological and 18FDG-PET studies. *Brain* 2006; 129: 668–75.
- Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308–14.
- Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. *Arch Neurol* 2006; 63: 1627–31.
- Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Forstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging* 2004; 25: 1051–6.
- Diehl-Schmid J, Grimmer T, Drzezga A, Bornschein S, Riemenschneider M, Forstl H, *et al.* Decline of cerebral glucose metabolism in frontotemporal dementia: a longitudinal 18F-FDG-PET-study. *Neurobiol Aging* 2007; 28: 42–50.
- DSM-IV-TR. Diagnostic and statistical manual of mental disorders. 4th edn., Washington, DC: American Psychiatric Association; 2000.
- Eckert T, Barnes A, Dhawan V, Frucht S, Gordon MF, Feigin AS, *et al.* FDG PET in the differential diagnosis of parkinsonian disorders. *Neuroimage* 2005; 26: 912–21.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–98.
- Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, *et al.* FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain* 2007; 130: 2616–35.
- Garraux G, Salmon E, Degueldre C, Lemaire C, Laureys S, Franck G. Comparison of impaired subcortico-frontal metabolic networks in normal aging, subcortico-frontal dementia, and cortical frontal dementia. *Neuroimage* 1999; 10: 149–62.
- Grimmer T, Diehl J, Drzezga A, Forstl H, Kurz A. Region-specific decline of cerebral glucose metabolism in patients with frontotemporal dementia: a prospective 18F-FDG-PET study. *Dement Geriatr Cogn Disord* 2004; 18: 32–6.
- Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. *Neurology* 2003; 61: 349–54.
- Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatry* 2000; 157: 172–8.
- ICD-10. International classification of diseases and related health problems (ICD-10). 10th edn., Geneva: World Health Organisation; 1992.
- Inagaki A, Iida A, Matsubara M, Inagaki H. Positron emission tomography and magnetic resonance imaging in spinocerebellar ataxia type 2: a study of symptomatic and asymptomatic individuals. *Eur J Neurol* 2005; 12: 725–8.
- Jeong Y, Cho SS, Park JM, Kang SJ, Lee JS, Kang E, *et al.* 18F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. *J Nucl Med* 2005; 46: 233–9.
- Jones CJ, Livson N, Peskin H. Longitudinal hierarchical linear modeling analyses of California Psychological Inventory data from age 33 to 75: an examination of stability and change in adult personality. *J Pers Assess* 2003; 80: 294–308.
- Josephs KA, Whitwell JL, Jack CR, Parisi JE, Dickson DW. Frontotemporal lobar degeneration without lobar atrophy. *Arch Neurol* 2006; 63: 1632–8.
- Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain* 2005; 128: 1996–2005.
- Kinahan PE, Rogers JG. Analytic 3D image reconstruction using all detected events. *IEEE Trans Nucl Sci* 1989; 36: 964–8.

- Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. *Dement Geriatr Cogn Disord* 2007a; 23: 334–42.
- Kipps CM, Nestor PJ, Dawson CE, Mitchell J, Hodges JR. Measuring progression in frontotemporal dementia: implications for therapeutic interventions. *Neurology* 2008; 70: 2046–52.
- Kipps CM, Nestor PJ, Fryer TD, Hodges JR. Behavioural variant frontotemporal dementia: not all it seems? *Neurocase* 2007b; 13: 237–47.
- Knopman DS, Boeve BF, Parisi JE, Dickson DW, Smith GE, Ivnik RJ, et al. Antemortem diagnosis of frontotemporal lobar degeneration. *Ann Neurol* 2005; 57: 480–8.
- Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh: E. & S. Livingstone; 1921.
- Kril JJ, Halliday GM. Clinicopathological staging of frontotemporal dementia severity: correlation with regional atrophy. *Dement Geriatr Cogn Disord* 2004; 17: 311–5.
- Kril JJ, Macdonald V, Patel S, Png F, Halliday GM. Distribution of brain atrophy in behavioral variant frontotemporal dementia. *J Neurol Sci* 2005; 232: 83–90.
- Malhi GS, Mitchell PB, Parker GB. Rediscovering chronic mania. *Acta Psychiatr Scand* 2001; 104: 153–6.
- Masdeu JC, Zubieta JL, Arbizu J. Neuroimaging as a marker of the onset and progression of Alzheimer's disease. *J Neurol Sci* 2005; 236: 55–64.
- Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000; 55: 1613–20.
- McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol* 2001; 58: 1803–9.
- McMurtry AM, Chen AK, Shapira JS, Chow TW, Mishkin F, Miller BL, et al. Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. *Neurology* 2006; 66: 517–22.
- McNeill R, Sare GM, Manoharan M, Testa HJ, Mann DM, Neary D, et al. Accuracy of single-photon emission computed tomography in differentiating frontotemporal dementia from Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2007; 78: 350–5.
- Meltzer CC, Kinahan PE, Greer PJ, Nichols TE, Comtat C, Cantwell MN, et al. Comparative evaluation of MR-based partial-volume correction schemes for PET. *J Nucl Med* 1999; 40: 2053–65.
- Mendhekar DN, Srivastav PK, Jiloha RC, Awana S. Chronic but not resistant mania: a case report. *Acta Psychiatr Scand* 2004; 109: 147–9.
- Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 1997; 42: 85–94.
- Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* 1997; 9 (Suppl 1): 173–6.
- Nagahama Y, Okina T, Suzuki N, Matsuda M. The Cambridge Behavioral Inventory: validation and application in a memory clinic. *J Geriatr Psychiatry Neurol* 2006; 19: 220–5.
- Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; 51: 1546–54.
- Nestor PJ, Caine D, Fryer TD, Clarke J, Hodges JR. The topography of metabolic deficits in posterior cortical atrophy (the visual variant of Alzheimer's disease) with FDG-PET. *J Neurol Neurosurg Psychiatry* 2003a; 74: 1521–9.
- Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage* 2006; 30: 1010–20.
- Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol* 2003b; 54: 343–51.
- Nestor PJ, Scheltens P, Hodges JR. Advances in the early detection of Alzheimer's disease. *Nat Med* 2004; 10 (Suppl): S34–41.
- Peters F, Perani D, Herholz K, Holthoff V, Beuthien-Baumann B, Sorbi S, et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. *Dement Geriatr Cogn Disord* 2006; 21: 373–9.
- Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 1979; 6: 371–88.
- Ravenna H, Jones C, Kwan VS. Personality change over 40 years of adulthood: hierarchical linear modeling analyses of two longitudinal samples. *J Pers Soc Psychol* 2002; 83: 752–66.
- Salmon E, Garraux G, Delbeuck X, Collette F, Kalbe E, Zuendorf G, et al. Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. *Neuroimage* 2003; 20: 435–40.
- Salmon E, Kerrouche N, Herholz K, Perani D, Holthoff V, Beuthien-Baumann B, et al. Decomposition of metabolic brain clusters in the frontal variant of frontotemporal dementia. *Neuroimage* 2006; 30: 871–8.
- Sato T, Bottlender R, Schroter A, Moller HJ. Psychopathology of early-onset versus late-onset schizophrenia revisited: an observation of 473 neuroleptic-naive patients before and after first-admission treatments. *Schizophr Res* 2004; 67: 175–83.
- Siegler IC, Dawson DV, Welsh KA. Caregiver ratings of personality change in Alzheimer's disease patients: a replication. *Psychol Aging* 1994; 9: 464–6.
- Strauss ME, Pasupathi M. Primary caregivers' descriptions of Alzheimer patients' personality traits: temporal stability and sensitivity to change. *Alzheimer Dis Assoc Disord* 1994; 8: 166–76.
- Terracciano A, Costa PT Jr, McCrae RR. Personality plasticity after age 30. *Pers Soc Psychol Bull* 2006; 32: 999–1009.