Functional neuroimaging and presenting psychiatric features in frontotemporal dementia

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Background: Frontotemporal dementia (FTD) is a behavioural syndrome caused by degeneration of the frontal and anterior temporal lobes. Behavioural disturbances include psychiatric features. Whether patients with FTD present with psychiatric features varies with the initial neuroanatomical variability of FTD.

Objective: To identify presenting psychiatric changes not part of diagnostic criteria for FTD and contrast them with the degree of hemispheric asymmetry and frontal and temporal hypoperfusion on single photon emission computed tomography (SPECT) imaging.

Methods: 74 patients who met consensus criteria for FTD were evaluated at a two year follow up. All had brain SPECT on initial presentation. Results of an FTD psychiatric checklist were contrasted with ratings of regional hypoperfusion.

Results: The regions of predominant hypoperfusion did not correlate with differences on FTD demographic variables but were associated with presenting psychiatric features. Dysthymia and anxiety were associated with right temporal hypoperfusion. "Moria" or frivolous behaviour also occurred with temporal lobe changes, especially on the right. The only significant frontal lobe feature was the presence of a peculiar physical bearing in association with right frontal hypoperfusion.

Conclusions: Patients with FTD may present with psychiatric changes distinct from the behavioural diagnostic criteria for this disorder. Early temporal involvement is associated with frivolous behaviour and right temporal involvement is associated with emotional disturbances. In contrast, those with right frontal disease may present with alterations in non-verbal behaviour.

Frontotemporal dementia (FTD) is a clinicopathological syndrome caused by progressive degeneration of the frontal lobes, anterior temporal lobes, or both.^{1–3} In contrast to other dementias, in FTD there is relative preservation of memory and visuospatial skills and early alterations in behaviour and personality.^{4–8} FTD patients have a social conduct disorder with inappropriateness, apathy, and passivity, a loss of emotions and empathy, and decreased insight.^{4–6, 8–9} Hyperorality or dietary changes and compulsive acts or stereotyped behaviours are additional common manifestations of early FTD.^{8–10–11}

These behavioural symptoms are the main features of the commonly used consensus criteria for the clinical diagnosis of FTD.⁵ In the absence of a biological marker for this disorder, clinicians diagnose FTD with these criteria, using neuroimaging and other test results as corroborative features.⁵ However, studies have shown that behavioural criteria are inadequate for the diagnosis of FTD on presentation and miss many psychiatric features.^{7–8–12} Up to two thirds of subsequently diagnosed cases of FTD lack all the required behavioural features of the consensus criteria on initial neurological or psychiatric presentation.⁷ Moreover, the first symptom of FTD may be depression, anxiety, or other psychiatric features not included among the behavioural criteria for this disorder.

The ability to determine when psychiatric changes indicate early FTD is crucial for its prompt recognition. Previous research has shown that a major variable determining the initial behavioural manifestations of FTD is the initial localisation of the disease.^{1–3} In the earliest stages, FTD is associated with significant hemispheric asymmetry and with a different extent of pathology in the frontal and anterior temporal regions.¹² Consequently, the presence of specific regional involvement on functional neuroimaging may

suggest which psychiatric features are the manifestations of FTD.

In this study we compared variations in functional neuroimaging and the nature of presenting psychiatric changes in a large series of FTD patients who eventually met the consensus criteria for FTD.⁵ The patients with FTD underwent single photon emission computed tomography (SPECT) on presentation. The study then compared the regions of SPECT hypoperfusion with ratings on six presenting psychiatric features, previously determined to be common in FTD but not included as part of the diagnostic criteria for the disorder.³

METHODS

Subjects

All participants presented for evaluation to university affiliated specialty clinics in dementing disorders. The patients underwent a comprehensive neurobehavioural evaluation, laboratory assessment, and magnetic resonance imaging (MRI) of the brain. The patients were screened for chronic mental illness, head trauma, extrapyramidal disorders, vitamin deficiency, hypothyroidism, syphilis, and other medical conditions. Finally, every subject underwent either technetium Tc99 m hexamethyl propylenamine oxime SPECT imaging as part of their initial diagnostic assessment.

All FTD patients included in the study presented with the insidious onset and progression of cognitive and behavioural changes and were followed up for at least a two year period. They were diagnosed with FTD if, at two years, they met clinical consensus criteria for FTD, with evidence of declines

Abbreviations: FTD, frontotemporal dementia; MMSE, mini-mental state examination; SPECT, single photon emission computed tomography

Table 1 Psychiatric checklist for frontotemporal dementia

After completion of the initial evaluation, determine the degree to which each of the following is a characteristic change in the patient's current state or behaviour, then place a number between 1 and 5* in the space provided:

- *Dysthymia*: feelings of sadness, low self esteem, self reproach, corresponding affect
- *Anxiety*: feelings of apprehension, fear, nervousness, fidgetiness
- *Psychotic symptoms*: delusions, paranoia, hallucinations, impaired reality testing
- *Anger or aggressive behaviour*: hostility, rage, verbal outbursts, physical outbursts
- *Moria or frivolousness*: childish or silly behaviour, facetiousness and Witzelsucht or a tendency to puns and jokes, flippant, fatuous and lacking seriousness
- *Peculiar physical bearing*: prolonged gaze, stare, or eye contact to the point of discomfort; an unchanging "fatuous" smile; abnormal or unchanging posture; physical behaviour inconsistent with the social context

*Scale: 1, not at all characteristic; 2, slightly characteristic; 3, moderately characteristic; 4, very characteristic; 5, extremely characteristic.

in social interpersonal conduct, regulation of personal conduct, emotional expression, and insight. We identified 74 FTD subjects who met these criteria at two years. None of the participants was significantly aphasic at the time of initial presentation; the study focused on patients who met behavioural criteria for FTD and did not include those who met criteria for primary progressive aphasia or semantic dementia.⁵ No subjects were receiving treatment with psychoactive drugs—including stimulants, depressants, neuroleptics, or other antipsychotic agents—at the time of the initial evaluation.

Procedures

Specialists evaluated the patients with an FTD psychiatric checklist on initial presentation (table 1). These features include dysthymia, distinguishable from apathy or the absence of feeling, interest, concern or motivation; anxiety, distinguishable from irritability; psychotic symptoms; anger or aggressive behaviour; "moria" (childish excitement or tendency to joke) or frivolous behaviour,³ distinguished from hypomania or mania; and changes in physical bearing, distinguishable from compulsive or repetitive behaviours. These items were included on the checklist because they were previously suggested to be common in FTD but were excluded from the initial diagnostic criteria.^{3–5} Neurologists completed the checklist after a structural interview with the patient and the informant. Most of the information came from the informant's report on changes in the patient's behaviour from their lifelong premorbid state. The investigators coded the items on the FTD psychiatric checklist a five point Likert scale from "Not at all characteristic" to "Extremely characteristic." The interrater reliability on the six checklist items for two participating neurologists was determined for six patients (weighted κ range, 0.438 to 0.573).

Table 2 Results of the FTD psychiatric checklist

FTD psychiatric checklist	Mean (SD)	Number* (%)
Dysthymia†	1.86 (1.38)	20 (27.0%)
Anxiety	2.08 (1.46)	22 (29.73%)
Psychotic symptoms	1.18 (0.45)	2 (2.70%)
Anger or aggressive behaviour	2.48 (1.27)	35 (47.30%)
Moria or frivolous behaviour	2.07 (1.41)	21 (28.38%)
Peculiar physical bearing	2.79 (1.51)	37 (50.0%)
Multiple symptoms	–	30 (40.54%)
All but psychotic symptoms	–	8
Dysthymia and anxiety	–	9
Anger/aggressive and moria	–	4

*Number scoring 3 or more (moderately to extremely characteristic) on the Likert scale.

†No patient had major depression sufficient to necessitate hospital admission.
FTD, frontotemporal dementia.

The SPECT scans were reread by two independent and experienced raters, blind to the clinical diagnosis. This technique has been reported previously.¹³ The blinded visual reinspections of the clinical SPECT scans used a quadrant approach. The raters initially graded the scans for hypoperfusion as absent, mild, moderate, or severe (on a 0 to 3 point scale) for each of left frontal, right frontal, left anterior temporal, and right anterior temporal regions. The combination of the two raters led to determination of whether the scans showed significant or non-significant involvement in each of the four regions of interest. For the two raters, the interrater reliability of the total SPECT hypoperfusion ratings was high ($r_s = 0.714$ for 296 ratings; $p < 0.001$).

Data analysis

Demographic characteristics were compared using two tailed t tests and χ^2 analysis as appropriate. Logistical regression was undertaken using the SPECT ratings as the independent variables and the checklist as the dependent variable. Preview of the FTD psychiatric checklist scores indicated a strongly bimodal distribution for all items except anger or aggressive behaviour, which showed a more normal distribution; thus the Likert scale results were dichotomised (1–2 v 3–5) for the logistical regression. Values are presented as mean (SD).

RESULTS

There were 36 men and 38 women, 68 right handed and six left handed, with 15.1 (3.2) years of education and minimal state examination (MMSE) scores of 22.6 (5.3).¹⁴ The age of onset was 57.7 (10.5) years, and the age of presentation was 60.9 (10.9) years. There were no differences based on sex or handedness on the SPECT rating scores or any of the six psychiatric features. There were no correlations between years of education, MMSE scores, age of onset, or age of presentation and either SPECT rating scores or any of the six items of the FTD psychiatric checklist.

Many of the patients with FTD had psychiatric changes on the FTD psychiatric checklist. Half of the FTD patients were scored 3–5 (moderately to extremely characteristic) on "peculiar physical bearing" and nearly half had anger or aggressive outbursts (table 2). Dysthymia, anxiety, and moria or frivolous behaviour were also common presenting symptoms, but psychotic features were unusual.

Prior analysis of the total SPECT hypoperfusion ratings for the two raters included means of 1.88 (0.95) for left frontal, 2.14 (0.90) for right frontal, 1.36 (0.79) for left temporal, and 1.73 (1.00) for right temporal regions. Among FTD patients who were rated with either moderate or severe (2 or 3) hypoperfusion on the SPECT scans, there were 59 with right frontal hypoperfusion, 50 with left frontal hypoperfusion, 44 with right temporal hypoperfusion, and 35 with left temporal hypoperfusion (Cochran's $Q = 17.65$, $df = 3$, $p < 0.001$).

There were several significant associations between four of the six psychiatric items and the SPECT regions of

Table 3 Logistical regression for significant associations

Region	χ^2	df	p Value
Dysthymia (likelihood ratio test: $\chi^2=69.77$, df 12, $p<0.001$)			
Right temporal	38.682	3	<0.001
Left frontal	6.738	3	NS
Right frontal	4.363	3	NS
Left temporal	0.916	3	NS
Anxiety (likelihood ratio test: $\chi^2=52.94$, df 12, $p<0.01$)			
Right temporal	21.416	3	<0.001
Left frontal	3.980	3	NS
Left temporal	1.743	3	NS
Right frontal	4.916	3	NS
Moria or frivolous behaviour (likelihood ratio test: $\chi^2=48.69$, df 12, $p<0.01$)			
Right temporal	18.999	3	<0.001
Left temporal	9.540	3	0.023
Left frontal	2.119	3	NS
Right frontal	1.544	3	NS
Peculiar physical bearing (likelihood ratio test: $\chi^2=35.68$, df 12, $p<0.01$)			
Right frontal	13.829	3	0.003
Left frontal	2.793	3	NS
Left temporal	2.973	3	NS
Right temporal	2.263	3	NS

hypoperfusion (table 3). Dysthymia and anxiety were associated with right temporal lobe hypoperfusion. Moria or frivolous behaviour occurred with temporal involvement, right relatively more than left. Peculiar physical bearing was associated with right frontal hypoperfusion. There were no significant SPECT associations for psychotic symptoms, anger, or aggressive behaviour.

DISCUSSION

Patients with FTD can present with psychiatric features which vary depending the regions that are involved early in the disease. Patients with FTD affecting predominantly the temporal lobes can present with emotional disturbances as well as with a personality change characterised by frivolous behaviour and lack of seriousness. In contrast, patients with FTD affecting predominantly the right frontal region can present with alterations in their non-verbal demeanour or bearing. These changes may be useful in the early diagnosis of FTD and in distinguishing FTD from primary psychiatric disorders.

Previous studies have shown that variability in the presenting behaviours in FTD depends on early variability in hemispheric or frontal or temporal pathology. Patients with left hemisphere FTD have early speech and language difficulty, and those with right hemisphere FTD manifest socially undesirable behaviour and a flattened and non-empathic affect.^{15–17} Patients with frontal FTD manifest apathy, decreased social dominance, and a dysexecutive personality change,^{17–19} and those with temporal FTD have impairments in emotional processing, interpersonal coldness, and hypomania-like behaviour.^{8 18 19}

FTD patients can also present with emotional disturbances such as dysthymia, anxiety, and anger or aggressive behaviour.^{20 21} Little previous research has focused on these symptoms in FTD. On the Neuropsychiatric Inventory, there are lower levels of depression among patients with FTD than in Alzheimer's disease.²² Depression, however, may be shallower in FTD than in Alzheimer's disease,²³ and dysthymia, rather than major depression, tends to occur in patients with temporal involvement.^{24 25} Anxiety is more common in FTD than in Alzheimer's disease,²⁶ and FTD patients can present with severe anxiety or panic attacks. Moreover, those with right temporal lobe involvement may

have increased levels of "neuroticism" and personal distress.²⁷ Anger and aggressive outbursts occur and may be more indicative of FTD than of Alzheimer's disease.²⁸ In this study, dysthymia and anxiety were particularly associated with the right temporal region. Although many of the FTD patients manifested anger and aggressive outbursts, there was no clear regional association on the SPECT scans.

The mechanism for these emotional disorders may relate to altered emotional reactivity. Although most FTD patients have emotional blunting and decreased empathy, those with temporal involvement are particularly at risk of developing deficits in emotional processing secondary to atrophy in the amygdala, anterior temporal cortex, and adjacent orbitofrontal cortex.²⁹ In addition, previous studies have suggested that predominantly right, as opposed to left, temporal involvement is more likely to be associated with emotional impairments in these patients.²⁹ In FTD, right temporal disease results in alterations in perception of facial and vocal emotions and affect, especially anger, sadness, and fear.^{30 31} Additional studies suggest that temporal lobe involvement in FTD spectrum disorders can result in exaggerated reactions to sensory stimuli.^{24 32}

Right temporal FTD often manifests profound changes in personality.^{15 16} These changes include abnormal social interactions, irritability, impulsiveness, acquired extroversion, decreased empathy, and sociopathic tendencies.^{15 16 19 33 34} In this study, there was an association of "moria," or frivolous excitement, with both right and left temporal hypoperfusion. This moria included childishness, silly facetiousness, flippant behaviour, fatuousness behaviour, and a lack of seriousness. Previously described in orbitofrontal lesions and in neurosyphilis, moria, and Witzelsucht—or excessive and inappropriate facetiousness and joking—can also be prominent in FTD.^{16 34} These behaviours may be especially related to disturbances in the anterior right temporal lobe and their connections or extension to the adjacent orbitofrontal region.³⁵

In contrast to the temporal lobe correlations, changes in physical bearing corresponded to right frontal hypoperfusion. Previous work has shown that aberrant motor behaviour is significantly more common among patients with FTD than in those with Alzheimer's disease.^{17 22} Although there is scant research on the physical bearing of these patients, case

descriptions indicate that some FTD patients manifest a sustained stare or “alien” stare, a fixed or “fatuous” smile, decreased spontaneous movements, and behaviour out of phase with their social context.^{3–36} FTD patients with right frontal involvement can also manifest other non-verbal behaviours such as simple stereotyped behaviours.¹⁰

The reasons are unclear for the relative infrequency of psychotic symptoms such as delusions and hallucinations in FTD. Despite rare case reports of FTD patients with a schizophrenia-like psychosis or a psychotic affective disorder,³⁷ delusional thoughts and hallucinations are uncommon in this disorder. In contrast, psychotic symptoms are common in Alzheimer’s disease.³ Among Alzheimer patients, the presence of frontotemporal pathology may facilitate delusions as a result of disturbed frontal systems for reality monitoring and testing, and disturbed temporal limbic systems for linking new experiences with past memories.³⁸ The difference may be that FTD patients have relative sparing of the temporal limbic system compared with Alzheimer patients.³¹

Conclusion

FTD presenting with psychiatric symptoms is disproportionately a temporal, especially right sided, disease. Affected patients manifest dysthymia, anxiety, moria or frivolous behaviour, and altered physical bearing. Although these findings are preliminary and need to be correlated with other psychiatric measures, they suggest additional behaviours that may be included as diagnostic criteria for FTD. Additional research, particularly in comparison with Alzheimer’s disease, can further clarify the relation between psychiatric features and regional brain involvement in patients with FTD.

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