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Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications

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Summary

A key aspect of social cognition is the ability to infer other people's mental states, thoughts and feelings; referred to as 'theory of mind' (ToM). We tested the hypothesis that the changes in personality and behaviour seen in frontal variant frontotemporal dementia (fvFTD) may reflect impairment in this cognitive domain. Tests of ToM, executive and general neuropsychological ability were given to 19 fvFTD patients, a comparison group of Alzheimer's disease patients (n = 12) and matched healthy controls (n = 16). Neuropsychiatric assessment was undertaken using the Neuropsychiatric Inventory (NPI). Patients with fvFTD were impaired on all tests of ToM (first-order false belief; second-order false belief; faux pas detection; and Reading the Mind in the Eyes), but had no difficulty with control questions designed to test general comprehension and memory. By contrast, the Alzheimer's disease group failed only one ToM task (second-order false belief), which places heavy demands on working memory. Performance on the faux pas test revealed a double dissociation, with the fvFTD group showing deficits on ToM-based questions and the Alzheimer's disease group failing memory-based questions only. Rank order of the fvFTD patients according to the magnitude of impairment on tests of ToM and their degree of frontal atrophy showed a striking concordance between ToM performances and ventromedial frontal damage. There was a significant correlation between the NPI score and more sophisticated tests of ToM in the fvFTD group. This study supports the hypothesis that patients with fvFTD, but not those with Alzheimer's disease, are impaired on tests of ToM, and may explain some of the abnormalities in interpersonal behaviour that characterize fvFTD.

Keywords: theory of mind; social cognition; frontotemporal dementia; Alzheimer's disease; neuropsychiatry

Abbreviations: ANOVA = analysis of variance; fvFTD = frontal variant frontotemporal dementia; MMSE = Mini-Mental State Examination; NC = normal control; NPI = Neuropsychiatric Inventory; OFC = orbitofrontal cortex; ToM = theory of mind; WCST = Wisconsin Card Sorting Test

Introduction

It has long been known that damage to the ventral or orbital frontal region can produce marked changes in personality and social functioning, including disinhibition, lack of empathy and self-centredness, social deviance, and difficulty with conversational pragmatics and in interpreting non-verbal cues (Eslinger and Damasio, 1985; Stuss and Benson, 1986; Dimitrov *et al*., 1999; Eslinger, 1999). Damage to the frontal lobes early in life also results in pervasive difficulties with social behaviour, decision-making, moral reasoning and empathy (Price *et al*., 1990; Scheibel and Levin, 1997; Anderson *et al*., 1999).

Amongst the dementias, the most striking changes of this type are found in patients with frontal lobe degeneration. The terminology applied to patients with non-Alzheimer pathology predominantly involving the frontal lobes is complex. Originally encompassed under the rubric of Pick's disease, more recently applied labels have been dementia of frontal type, frontal lobe dementia, frontotemporal dementia and

frontotemporal lobar degeneration (Snowden *et al*., 1996; Neary *et al*., 1998). In our recent studies, we have adopted the term frontal variant frontotemporal dementia (fvFTD) to denote patients with predominant involvement of the frontal lobes, rather than the temporal variant which results in loss of semantic knowledge and a progressive fluent aphasic syndrome (Gregory, 1999; Gregory *et al*., 1999; Hodges *et al*., 1999; Rahman *et al*., 1999; Bozeat *et al*., 2000; Perry *et al*., 2000; Hodges and Miller, 2001*a*, *b*).

Patients with fvFTD present in their 50s and 60s with insidious changes in personality and behaviour, including lack of empathy or concern for others, apathy, socially inappropriate and disinhibited behaviour, impaired personal awareness and loss of insight (Lund and Manchester Groups, 1994; Gregory and Hodges, 1996*a*). There is also a marked tendency to develop stereotypic or ritualized patterns of behaviour, reminiscent of those seen in autism (Bozeat *et al*., 2000). Patients with fvFTD can, in the early stages of the disorder, cause considerable diagnostic doubt. Despite the gross alterations in interpersonal behaviour, patients may perform normally on traditional frontal executive tasks which we have suggested reflects the known orbitofrontal focus of the pathology in fvFTD (Gregory *et al*., 1999; Rahman *et al*., 1999). Frontal executive tasks, while sensitive to dorsolateral prefrontal pathology, are relatively insensitive to the orbitofrontal degeneration seen in fvFTD.

Developmentally, one of the cognitive abilities that enables children to engage in social behaviour is 'theory of mind' (ToM), i.e. the ability to infer other people's mental states, thoughts or feelings. ToM has a number of features that suggest that it is a domain-specific social cognitive ability, not just the result of general reasoning abilities applied to the social world: (i) it goes through a stereotypical development sequence increasing in complexity through childhood; (ii) the dissociation seen from other areas of mental function. For example, in Down's and William's syndromes, individuals perform in line with mental age on ToM tasks while, in individuals with autism and Asperger's syndrome, performance on ToM tasks is disproportionately impaired compared with their mental age (Tager-Flusberg, 1993; Baron-Cohen, 1995; Baron-Cohen *et al*., 1999*a*). The fact that ToM tasks also place heavy demands upon executive function has led some authors to suggest that deficit in ToM in autism might result from an executive function deficit (Griffith *et al*., 1999). Recent research, however, has found no evidence for an early executive function deficit in autism (Griffith *et al*., 1999), and administering executive tasks by computer rather than by a person improves the performance of people with autism (Griffith, 2001). Furthermore, people with autism are also impaired on ToM tasks that do not have an executive component (Baron-Cohen, 1995; Baron-Cohen *et al*., 1997). Thus, even in autism, there is still a dissociation between ToM and other cognitive abilities. Though ToM may not be the sole 'core deficit' in autism, ToM deficits do appear to underlie the social deficits in individuals with high functioning autism and Asperger's syndrome. This fact led us to investigate whether ToM deficits might be involved in patients with frontotemporal dementia.

Neuroimaging studies primarily implicate the frontal lobes in ToM, although the exact area of activation has varied across different experimental paradigms. Other brain regions such as the limbic system, particularly the amygdala, may also be involved in ToM (Baron-Cohen *et al*., 1994, 1999*b*; Stone, 2000; Fine *et al*., 2001). Baron-Cohen *et al*. (1994) found orbitofrontal cortex (OFC) activation using SPECT (single-photon computerized tomography) during a simple ToM test requiring recognition of words that have to do with the mind, e.g. 'remember', 'thought', but not during a test requiring recognition of body terms, e.g. 'jump', 'arm'. Using PET, Goel *et al*. (1995) found medial frontal and left temporal activation during a task requiring belief attribution, while Fletcher *et al*. (1995) found activation in Brodmann areas 8 and 9 in the left medial frontal cortex during a task measuring understanding of deception and belief attribution. A recent study by Gallagher *et al*. (2000), using fMRI (functional MRI) and an experimental paradigm that employed both non-verbal (cartoons) and verbal material to tap ToM, showed considerable overlap, specifically in the medial frontal cortex (paracingulate cortex). It is difficult to obtain reliable activation maps for the OFC using fMRI, so such studies cannot illuminate the role of this region in ToM.

Evidence for the neural basis of ToM from the study of brain-injured adult subjects is, so far, limited but suggests that certain regions within the prefrontal cortex may be critical. In one study, patients with unilateral dorsolateral prefrontal lesions performed normally on first- and second-order belief tests and tests of faux pas recognition. In contrast, patients with OFC lesions, although able to pass the first- and second-order belief tests, were significantly impaired on tests of faux pas recognition and recognizing complex mental and emotional states from pictures of the eyes (Stone *et al*., 1998, Stone, 2000). Baron-Cohen *et al*. (1994) and Stone *et al*. (1998) proposed that ToM abilities are underpinned by a distributed system involving many regions of the prefrontal cortex and limbic system, including the OFC. More recently, Stuss *et al*. (2001) found deficits in visual perspective-taking and detection of deception in patients with acquired frontal and non-frontal lobe damage. Medial frontal lesions, particularly right ventral, impaired detection of deception.

To our knowledge, there are no reported studies that have examined ToM in patients with frontal lobe dementia. Assessment of performance on ToM tests in patients with fvFTD may be relevant in understanding the genesis of the change in social interaction and may assist in earlier diagnosis. The major aim of our study was to test the hypothesis that patients with fvFTD would show impairments on tests of ToM. To establish whether any detected deficits in ToM are specific to fvFTD, we also studied a matched group of patients with Alzheimer's disease. In Alzheimer's disease, there is profound impairment of episodic memory followed by breakdown in semantic and attentional processing, but personality and social conduct typically are well preserved.

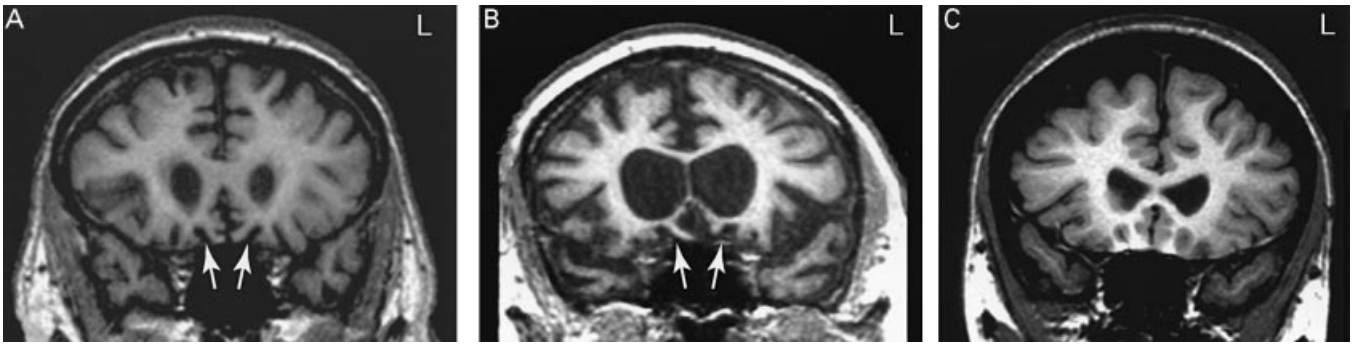

Fig. 1 Coronal MRI scans at the level used to rate degree of ventromedial and dorsolateral frontal atrophy. (**A**) Mild ventromedial atrophy (arrows). (**B**) Severe ventromedial (arrows) and moderate dorsolateral atrophy. (**C**) A comparable normal individual. L = left hemisphere.

Secondary aims were to investigate the relationship between performance on the tests of ToM, traditional frontal executive tasks and the degree of neuropsychiatric and behavioural dysfunction in fvFTD.

Methods

Ascertainment of patients

A total of 47 participants were included in the study and consisted of 19 patients with frontotemporal dementia (16 males and three females, age range 44–67 years, mean 58.6 ± 6.9 years), 12 with Alzheimer's disease (six males and six females, age range 52–79 years, mean 66.5 ± 8.9 years) and 16 healthy control volunteers (eight males and eight females, age range 52–76 years, mean 57.1 ± 5.1 years). A professor of behavioural neurology (J.R.H.), a senior psychiatrist (C.G.) and a consultant psychologist (S.L.) assessed all of the patients, who were seen at the Early Onset Dementia Clinic at Addenbrooke's Hospital, Cambridge between 1998 and 2000. A thorough history was taken from the patient and from a close relative/carer. Patients underwent routine haematology, biochemistry, tests of thyroid function, screening tests for syphilis, examination of the CSF and a thorough physical examination. All patients received structural neuroimaging, either CT or MRI scan, and functional neuroimaging using HMPAO-SPECT.

All patients presented with a corroborated history of progressive change in personality and behaviour and fulfilled the Lund–Manchester consensus criteria for frontotemporal dementia (Neary *et al*., 1998) plus our locally developed criteria applied in previous studies (Gregory *et al*., 1999; Rahman *et al*., 1999; Bozeat *et al*., 2000; Perry *et al*., 2000). Patients presenting primarily with language complaints (progressive non-fluent aphasia or semantic dementia), or those showing a significant degree of semantic impairment that might interfere with their comprehension of tasks were excluded.

All Alzheimer's disease subjects fulfilled NINCDS-ADRDA (National Institute of Neurological and Communicable Diseases and Stroke-Alzheimer's Disease and Related Disorders Association) criteria for probable Alzheimer's disease (McKhann *et al*., 1984). The fvFTD and Alzheimer's disease groups were matched on the basis of their Mini-Mental State Examination (MMSE) scores. Sixteen age- and years of education-matched controls, selected from the volunteer panel at the Medical Research Council Cognition and Brain Sciences Unit, underwent full neuropsychological assessment, and 10 of these were used as controls for the ToM tests.

The study was approved by the Cambridge local ethics committee and informed consent was obtained from the patients and relatives, and from control participants.

Assessment of brain atrophy on MRI

In 17 out of the 19 fvFTD subjects recent MRI scans were available. To assess the degree of frontal atrophy in the fvFTD group, we devised a visual rating scale similar in concept to our recently described anterior temporal lobe rating scale; the latter has been validated against volumetric analyses (Galton *et al*., 2001). The frontal ratings were undertaken using T_1 coronal images through the frontal and anterior temporal lobes on slices that clearly showed the gyrus rectus before the appearance of the basal ganglia structures (see Fig. 1). Two regions were assessed, the ventromedial (orbital) and the dorsolateral prefrontal cortex, using a four point scale (3 = severe atrophy, 2 = moderate, 1 = mild, 0 = no atrophy). Questionable cases were coded as 0. Patient scans were anonymized and assessed together with the scans from 15 normal age-matched control subjects by one highly experienced rater (J.R.H.) on two separate occasions. Normal controls obtained scores of 0 in 24 out of 30 instances; all other scores were 1. For patients, there was generally good, but not excellent, intra-rater agreement ($\kappa = 0.67$). Most discrepancies were differences of 1 point only. When dichotomized as abnormal (score 3 or 2) versus normal (score 1 or 0), there was excellent agreement ($\kappa = 0.8$).

General neuropsychological test battery

Tests given were the MMSE (Folstein *et al*., 1975) and the Addenbrooke's Cognitive Examination (ACE) (Mathuranath

et al., 2000) as a general assessment of cognitive function; digit span forward and backwards; the logical memory (story recall) subtest from the Wechsler Memory Scale—Revised (Wechsler, 1987); the Rey Complex Figure Test Copy and 45 minute recall (Rey, 1941); components of the Visual Object and Space Perception (VOSP) battery (Warrington and James, 1991); the Graded Naming Test (McKenna and Warrington, 1983); the Pyramid and Palm Trees Test of associative semantic knowledge (Howard and Patterson, 1992); verbal fluency for words beginning with the letters F, A and S (Benton, 1968); and the Wisconsin Card Sorting Test (WCST), modified version (Nelson, 1976).

Neuropsychiatric assessment

All carers of fvFTD and Alzheimer's disease patients completed the Neuropsychiatric Inventory (NPI), a semi-structured clinician-led interview. Testers used the protocol described by Cummings *et al*. (1994) after training using the video made available to us by the authors. This schedule probes 12 areas of behaviour and neuropsychiatric functioning: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour and appetite disturbance. Each item is scored according to the frequency (f) of its presence (on a scale of 0–4) and the severity (s) of the disturbance (scale of 0–3), producing a total score f $\times$ s. Thus the highest score achievable is 144.

Theory of mind tests

We selected four ToM tasks that could be ordered in terms of developmental complexity and difficulty: a first-order false belief task; a second-order false belief task; a recognition of faux pas task; and the Reading the Mind in the Eyes Task (Baron-Cohen *et al*., 1997). First-order false belief tasks can be solved by children between the ages of 3 and 4 years, showing that they understand that others may have different mental states from themselves and may therefore hold a false belief (Dennett, 1978; Wimmer and Perner, 1983). From the age of 6 years, children begin to understand second-order false belief, i.e. that someone may hold false beliefs about someone's beliefs (Perner and Wimmer, 1985). Between the ages of 9 and 11 years, children develop an understanding of 'faux pas', i.e. recognizing when someone says something unintentionally that they should not have said because it is meant to be confidential or could be hurtful (Baron-Cohen *et al*., 1999*a*). Finally, the ability to recognize complex emotions and mental state from facial expression, in particular solely from the eyes, has been postulated recently as an advanced aspect of ToM that emerges around the time of adolescence (Baron-Cohen *et al*., 1997, 1999*c*).

First-order false belief test

This task is designed to assess subjects' ability to infer that someone has a (mistaken) belief that is different from the subject's own (true) belief (Wimmer and Perner, 1983; Baron-Cohen *et al*., 1985). The examiner describes (using illustrative photos that are placed in front of the subject and remain there during test questions) a story in which two people are in a room together. In the story, Person 1 places an object in a given location, witnessed by Person 2. Something is spilled or leaves a mark at this location. Person 1 then leaves the room. The second person moves the object to another location while the first person is out of the room. The first person then returns to the room. The subject is then asked a series of questions about the story. Firstly, the *belief* (ToM) question, i.e. where Person 1 thinks the object is. Secondly, the *reality* question which checks that the subject recalls where the object really is at the end of the story. Thirdly, a *memory* question, i.e. where the object was at the beginning of the scenario. Finally, an *inference* question asks where there would be, for example, a spill mark. Scores for the latter three control non-ToM tasks were combined. Details of this task are given elsewhere (Stone *et al*., 1998). Four stories are described in this way. Scores were calculated as proportions since not all subjects received all four stories.

Second-order false belief task

This task is based on Perner and Wimmer (1985) and Baron-Cohen (1989). It again consists of a scenario described to the subject, illustrated with photographs that the individual may refer back to. In each story, Person 1 puts an object in a location witnessed by Person 2, Person 1 then leaves the room. While Person 1 is out of the room, Person 2 moves the object but, unbeknown to Person 2, Person 1 is peeking back into the room and sees the object being moved. The subject is then asked a *second-order belief* (ToM) 'when Person 1 re-enters the room, where will Person 2 think that Person 1 thinks the object is?' There is also a *reality* question, a *memory* question and an *inference* question. Scores for the three non-ToM questions were combined. As before, four scenarios are presented and the pictures remain in front of the subject during the test questions. In order to answer the second-order belief question correctly, the subject has to be able to represent not only each person's belief about the location of the object, but also understand Person 2's mistaken belief about Person 1's belief.

Faux pas test (Stone et al., *1998; Baron-Cohen* et al., *1999*a*)*

In this test, the subject is read 10 stories that contain a social faux pas and 10 control stories that contain a minor conflict, but in which no faux pas is committed. This is a methodological improvement over the version of the task used previously (Stone *et al*., 1998). The text of each story is also

placed in front of the subject so that it may be referred to, thereby reducing the demands made on working memory. After each story, the subject is asked if anyone said something that they should not have said, i.e. to identify correctly the stories containing a faux pas. If a faux pas is identified, two clarifying questions are asked: 'Why shouldn't they have said what they did' and 'Why do you think they did say it?' (see Appendix I for an example). In order to comprehend that a faux pas has occurred, the subject has to understand two mental states: namely that the person making the faux pas does not, at that moment, *know* that they should not say it; and, that the person hearing it would be upset or hurt to discover the informant. In the control stories, no faux pas is committed but all of the same questions are asked of the subject. In all stories, regardless of the subject's answer to the first question, non-ToM based memory questions are asked to assess the subject's story comprehension. Subjects were encouraged to answer all of the questions but were not prompted. A few ($n = 3$) of the fvFTD group were unable to complete all of the stories due to their limited tolerance of testing.

Reading the Mind in the Eyes Test (Baron-Cohen et al., *1997)*

This task consists of photographs of the eye region of 25 faces. The subject is required to make a choice between two words printed at the bottom of the page on which the picture appears and to choose the one that best describes what the individual in the photograph is thinking or feeling (e.g. 'ignoring you' versus 'noticing you'). This test places no memory demands on the subject. The original version of this adult test was used since the revised version was not available at the time of testing (Baron-Cohen *et al*., 2001).

Statistical analysis

Statistical analyses were performed using SPSS. Group comparisons employed analysis of variance (ANOVA) with *post hoc* pairwise comparisons using Tukey's test or unpaired *t*-tests as appropriate. Parametric statistics were used since an initial exploration of the data set suggested an acceptable distribution (Skewness < 1.00, Kurtosis < 3.00). In view of the difference in age and education between the groups, comparison of the key ToM variables was performed using analysis of covariance (ANCOVA). In all instances, there were no main effects of age or education and all intra-group differences remained significant. To examine the relationship between tests of ToM executive function and NPI scores, we calculated Pearson's correlation coefficients. For the concordance between extent of brain atrophy and ToM performance, we used Spearman's rho rank-order statistic. Patients were classified as impaired if their score fell below 1.5 SDs of the control group's mean performance.

Results

General neuropsychological data (Table 1)

The groups were well matched in terms of level of MMSE, digit span forwards and backwards ($P > 0.05$). The fvFTD and Alzheimer's disease groups performed at a similarly impaired level on the Addenbrooke's Cognitive Examination ($P > 0.05$). On tests of episodic memory, there were main group effects on all measures ($P < 0.01$): for immediate and delayed story recall (logical memory) and delayed recall of the Rey figure, *post hoc* analyses showed the Alzheimer's disease group to be impaired relative to both the fvFTD and normal control (NC) groups, with no difference between the latter two groups (Alzheimer's disease < fvFTD = NC). On tests of visuospatial function (copy of the Rey figure and components of the Visual Object and Space Perception Battery), there were no significant intra-group differences. The two tests of semantic memory showed a slightly different pattern: on the Graded Naming Test, there was a small but significant difference between the fvFTD group and the other groups ($P < 0.05$; fvFTD < Alzheimer's disease = NC), but a comparison of the three groups on the Pyramids and Palm Trees Test revealed no intra-group difference. As might be predicted, performance on tests of executive function (F, A, S word fluency and the WCST) was significantly worse in the fvFTD group than in controls, with no difference between the Alzheimer's disease group and controls (fvFTD < Alzheimer's disease = NC).

Neuropsychiatric Inventory

For the fvFTD group, scores on the NPI ranged from 5 to 74 (mean of 49.0 ± 17.2). Fifteen patients had a score over 40. One patient had a low score (5). This patient had recently stopped working and under the closer supervision of his wife many of his behaviours had settled considerably. During the interview, his wife also reported that 'she had got used to him'. A second patient had a relatively low score of 16. In his case, no carers were available; family members had become estranged because of his difficult behaviour. Information for the NPI was supplied by nursing staff on the psychiatric ward where he had been hospitalized for assessment, a ward on which there was considerable tolerance of disturbed and inappropriate behaviour. This factor may have resulted in a lower NPI score than would have been provided by a carer in a home-based setting. The Alzheimer's disease group had generally low scores (mean 5.2 ± 5.7; range 0–18), with only two patients scoring over 10 while seven scored below 5. The difference in scores between the fvFTD and Alzheimer's disease groups was highly significant [$t(27) = 7.8$, $P < 0.001$].

ToM tests

First-order false belief test (Table 2)

Scores for each individual were calculated as the proportion of belief questions correct out of the total number of stories

Table 1 *Demographic data and performance on general neuropsychological tests*

	FvFTD (19)	Alzheimer's disease (12)	Controls (16)	ANOVA *F* value (d.f.) and *post hoc* comparisons
Age (years)	58.6 (6.9)	66.5 (8.9)	57.1 (5.1)	6.79 (2,44)**,†
Education years	11.6 (2.2)	14.4 (4.0)	12.1 (1.5)	4.80 (2,44)*,†
NART IQ	105.6 (13.9)	116.7 (11.5)	116.5 (8.9)	4.77 (2,43)*,‡
MMSE	26.6 (3.2)	27.1 (1.7)	28.7 (1.0)	NS (2,44)
ACE	81.4 (10.2)	82.2 (5.3)	–	NS (*t*-test)
NPI	49.0 (17.1)	5.2 (5.7)	–	** (*t*-test)
Memory				
Digit Span Forwards	6.0 (1.6)	6.1 (1.0)	7.0 (1.0)	NS (2,43)
Digit Span Back	4.7 (1.5)	4.6 (1.2)	5.2 (1.4)	NS (2,43)
Logical memory				
Immediate	8.8 (4.0)	5.5 (2.8)	9.1 (2.3)	4.51 (2,40)*,‡
Delayed	6.4 (3.7)	1.7 (2.7)	7.1 (2.4)	10.62 (2,39)***,§
Rey Figure recall	14.3 (8.1)	6.5 (5.7)	19.0 (5.7)	11.35 (2,39)**,§
Visuospatial				
Rey Copy	32.2 (4.4)	31.9 (4.5)	34.2 (1.6)	NS (2,41)
VOSP				
Incomplete letters	18.5 (2.2)	19.0 (1.6)	19.3 (0.8)	NS (2,40)
Object decision	16.8 (2.9)	17.9 (2.8)	17.2 (2.1)	NS (2,37)
Position discrimination	18.3 (3.4)	NA	19.7 (0.8)	NS (2,27)
Semantic				
Graded Naming	18.8 (6.4)	22.4 (4.5)	24.9 (2.9)	6.5 (2,42)**,‡
PPT pictures	49.0 (3.9)	50.6 (2.8)	51.1 (0.8)	ns (2,44)
Executive				
FAS	27.1 (13.0)	44.1 (11.4)	38.7 (10.2)	7.81 (2,41)**,‡
WCST categories	4.4 (1.7)	5.3 (0.7)	5.7 (0.6)	5.02 (2,38)*,‡
WCST perseverative errors	8.94 (9.5)	4.5 (3.0)	1.1 (2.6)	5.69 (2,37)**,‡

*$P < 0.5$; **$P < 0.01$; ***$P < 0.001$; †fvFTD and controls significantly different from Alzheimer's disease; ‡fvFTD significantly different from both Alzheimer's disease and controls; §Alzheimer's disease significantly different from fvFTD and controls; ACE = Addenbrooke's Cognitive Examination; MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; NPI = Neuropsychiatric Inventory; PPT = Pyramids and Palm Trees Test; VOSP = Visual Object and Space Perception; WCST = Wisconsin Card Sorting Test.

Table 2 *Performance on theory of mind tasks by frontal variant FTD dementia (fvFTD), Alzheimer's disease and control subjects, showing mean (± standard deviation) scores*

	fvFTD	Alzheimer's disease	Controls	ANOVA *F* value (d.f.) and *post hoc* comparisons
First-order false belief				
ToM questions	0.80 (0.3)	0.98 (0.1)	1.0	5.26 (2,44)**†
Control questions	0.95 (0.1)	0.94 (0)	1.0	NS (2,44)
Second-order false belief				
ToM questions	0.74 (0.4)	0.78 (0.3)	1.0	4.53 (2,41)*‡
Control questions	0.98 (0.1)	0.94 (0.1)	1.0	NS (2,41)
Faux pas stories				
Faux pas correct (hits)	0.67 (0.3)	0.88 (0.1)	0.95 (0.1)	9.72 (2,44)***†
Correct rejects	0.73 (0.3)	0.85 (0.1)	0.99 (0.1)	7.48 (2,44)**†
Composite score	0.60 (0.2)	0.83 (0.1)	0.94 (0.1)	22.10 (2,44)***†
Control questions	0.88 (0.1)	0.77 (0.2)	0.99 (0.1)	6.87 (2,44)**§
Reading the Mind in the Eyes	0.64 (1.7)	0.79 (1.3)	0.79 (1.0)	6.31 (2,31)**†

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; †fvFTD impaired versus Alzheimer's disease and controls; ‡fvFTD and Alzheimer's disease impaired versus controls; §Alzheimer's disease impaired versus fvFTD and controls.

used for that subject (three fvFTD patients were not administered all four stories). Controls performed perfectly on this task, scoring 1.0. Seven out of the 19 fvFTD patients (37%) showed deficits, the rest performed perfectly. Only one out of the 12 Alzheimer's disease patients scored below 100%. As a group, fvFTD patients achieved a mean score of 0.80 (±0.3) compared with 0.98 (±0.1) for the Alzheimer's disease group. A one-way ANOVA revealed a highly

Table 3 *Consistency across ToM tasks and relationship to extent of atrophy of ventromedial (VM) and dorsolateral prefontal cortex (DLPFC) assessed from coronal MRI*

	First-order false belief	Second-order false belief	Faux pas	Mind in Eyes	No. of ToM deficits	Brain atrophy	
						VM	DLPFC
M.W.	+	+	+	+	4	+++	++
P.L.	+	+	+	+	4	++	+
M.R.	+	+†	+	+	4	++	+++
C.D.	+	+	+	+	4	++	0
I.B.	+	+	+	0	3	+++	+++
J.Mc.C.	+	+	+	0	3	++	+
P.E.	0	+	+	+	3	+++	++
T.R.	0	+$	+	+	3	++	+
J.W.	0	+	+	0	2	++	+
J.L.	+	0	+	0	2	+	++
J.M.	0	0	+	+	2	0	0
C.B.	0	0	+	0	1	1	0
H.D.	0	0	+	0	1	NA	
J.G.	0	0	+	0	1	NA	
P.B.	0	0	0	+	1	0	0
W.L.	0	0	0	0	0	0	0
R.L.	0	0	0	0	0	0	0
N.S.	0	0	0	0	0	+	0
T.A.	0	0	0	0	0	+	0
Total impaired	7	9	14	8	15	13/17	9/17

NA = not available; † = patient was unable to comprehend the concept of the task (see the text); + = impaired.

significant group difference ($P < 0.01$). *Post hoc* analyses confirmed a significant difference between the fvFTD group and the other two groups ($P < 0.05$; fvFTD < Alzheimer's disease = NC). Neither patient group exhibited any difficulty with the non-ToM questions (fvFTD = 0.95 ± 0.1, Alzheimer's disease = 0.94 ± 0, NC = 1.0; $P > 0.05$).

Second-order false belief test

Two fvFTD patients were unable to understand the concept of the second-order false belief tasks, which had to be abandoned after a few trial stories, leaving 17 patients who were able to complete the task. The scores on this task were calculated by taking the proportion of second-order belief questions correctly answered out of the total number of stories used for that subject. Thus nine out of 19 (47%) patients made errors ($n = 7$) or could not understand the task ($n = 2$); the rest performed perfectly. Six out of the 12 Alzheimer's disease (50%) patients also showed deficits. Again controls performed at ceiling (mean score of 1.0). Comparison of the three groups' mean scores showed a highly significant difference (fvFTD = 0.74 ± 0.4, Alzheimer's disease = 0.78 ± 0.3, controls = 1.0; $P < 0.05$) but *post hoc* pairwise analyses revealed no difference between fvFTD and Alzheimer's disease groups (fvFTD = Alzheimer's disease < NC). As with the first-order false belief task, neither patient group had difficulty with the 'control' non-ToM questions (fvFTD = 0.98 ± 0.1, Alzheimer's disease = 0.94 ± 0.1, NC = 1.0; $P > 0.05$).

Faux pas test

Patients' answers were scored by two independent raters, V.S. and S.L. Inter-rater reliability was excellent, $r = 0.98$. Table 2 shows the scores for the proportion of faux pas correctly detected (i.e. hits) and the proportion of correct rejections of faux pas in the control (non-faux pas) stories (i.e. correct rejects). A composite score was also calculated as follows: total hits plus total number of clarifying questions related to the faux pas answered correctly plus the number of correct rejects divided by the number of faux pas (×3) plus control questions given. Finally, the proportion of non-ToM (memory-based) questions correctly answered was calculated. Three fvFTD subjects did not receive all of the stories due to their reduced tolerance of testing. Scores for all stories administered were included in the analysis.

The proportion of faux pas correctly detected by the fvFTD group (0.67 ± 0.3) was significantly less than that for the other two groups, with no difference between Alzheimer's disease patients and controls (0.88 ± 0.1 versus 0.95 ± 0.1, respectively: $P < 0.001$; fvFTD < Alzheimer's disease = NC). Similarly, the fvFTD group had a significantly higher rate of false positive endorsement on the stories containing no faux pas, as reflected in the correct reject scores (0.73 ± 0.3 versus 0.85 ± 0.1 and 0.99 ± 0.1 for Alzheimer's disease and NC, respectively: $P < 0.001$; fvFTD < Alzheimer's disease = NC). Even when a faux pas was detected correctly, patients often made errors on the clarifying questions, such as recognizing that the faux pas had been unintentional. Thus the same pattern was maintained for the composite score:

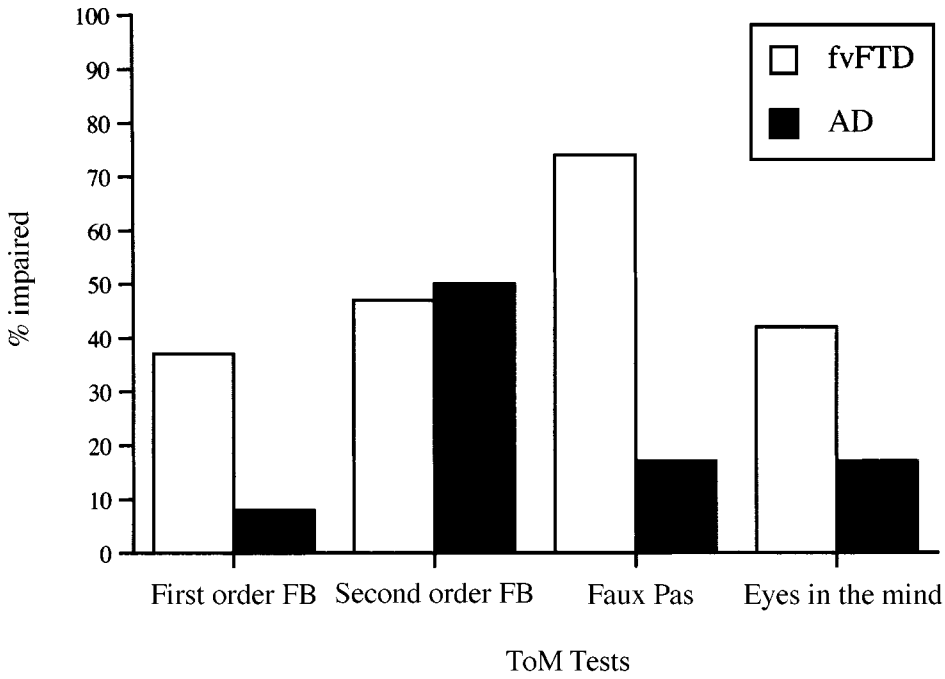

Fig. 2 Proportion of patients in the frontal variant frontotemporal dementia (fvFTD) and Alzheimer's disease (AD) groups showing impairment on the first-order false belief (FB), second-order false belief, faux pas and Reading the Mind in the Eyes Test.

fvFTD < Alzheimer's disease = NC. Based upon the latter score, 14 out of the 19 (74%) fvFTD patients showed impairment compared with only two out of 12 (17%) Alzheimer's disease patients. By contrast, the opposite pattern was observed on the non-ToM (memory-based) component. An ANOVA showed a significant intra-group difference, and *post hoc* comparison confirmed that the Alzheimer's disease group was impaired (0.77 ± 0.2) relative to the fvFTD (0.88 ± 0.1) and control (0.99 ± 0.1) groups, with no difference between the latter two ($P < 0.01$; Alzheimer's disease < fvFTD = NC).

Reading the Mind in the Eyes Test

One-way ANOVA revealed a significant intra-group difference ($P < 0.01$), with the fvFTD group performing worse than both the Alzheimer's disease and the control groups (fvFTD < Alzheimer's disease = NC). Eight out of 19 fvFTD patients' scores (42%) fell in the impaired range compared with two out of the 12 Alzheimer's disease cases (17%).

Summary of ToM tests

Figure 2 illustrates the proportion of fvFTD and Alzheimer's disease patients showing impairment on the ToM tasks. It can be seen that the fvFTD patients showed progressively greater impairment across the two false belief and faux pas tests, with 74% of cases falling below normal on the latter test. The degree of impairment on the Reading the Mind in the Eyes Test was equivalent to that in the second-order false belief test. The fvFTD group, by contrast, had no difficulty with the control (non-ToM) questions. The Alzheimer's disease group performed generally well on all ToM tasks and showed significant deficits on the second-order false belief only. On the most sensitive ToM task, the faux pas test, they were unimpaired on ToM-based questions but, unlike fvFTD patients, they failed a significant number of control questions.

Consistency across ToM tasks and relationship to extent of brain atrophy in FTD

Table 3 examines the concordance between the various ToM tasks used in the study on an individual case-by-case basis. It can be seen that 15 out of the 19 fvFTD (79%) patients showed impairment on one or more of the ToM tasks. When considered according to the sensitivity of the tasks, there was a striking consistency, with a gradual accumulation of deficits across the first three ToM tasks. For instance, of the nine patients showing deficits on the second-order false belief test, all nine were also impaired on the faux pas test; plus there were an additional five patients who were also impaired on the faux pas test but had performed normally on the former tests. Formal correlational statistics showed considerable intercorrelation between the ToM tasks: the first-order false belief test correlated with the second-order false belief test ($r = 0.67$, $P = 0.01$) and with the faux pas test ($r = 0.76$, $P = 0.003$). The second-order false belief test also correlated

with the faux pas test ($r = 0.78$, $P = 0.001$). The exception to this was the Reading the Mind in the Eyes Test, which did not correlate significantly with the other ToM tasks.

As described above, the extent of brain atrophy was assessed using a visual rating scale based upon the extent of ventromedial (orbital) and dorsolateral prefrontal atrophy. It can be seen that in virtually all cases, the extent of atrophy was greatest in the ventromedial region (as illustrated in Fig. 1). There was also a close correspondence between the severity of atrophy and the degree of impairment on tests of ToM (the latter was judged by the number of tests on which the patient showed deficits). Rank order analysis confirmed a highly significant association between ToM and the degree of frontal atrophy (ventromedial $r = 0.63$, $P = 0.002$; dorsolateral $r = 0.57$, $P = 0.007$).

From the perspective of clinical diagnosis, it should be noted that several patients showed impairment on at least one ToM task yet had apparently normal MRI scans when assessed visually.

Correlation between ToM, executive function and neuropsychiatric symptoms

We were interested to examine whether the fvFTD patients' performance on the ToM tests would be correlated with traditional tasks of frontal executive neuropsychological function, measures of semantic memory and general intellectual performance (i.e. the MMSE) or with measures of behavioural or psychiatric disturbance, as judged by scores on the NPI. Correlations significant at the 0.05 level (two-tailed) and at the 0.01 level were found for a number of variables.

Considering the relationship between ToM and frontal executive function, the only significant correlation was between the faux pas test and the number of perseverative errors on the WCST. None of the other executive function, semantic memory or general intellectual measures were correlated with ToM performance.

Finally, there was a significant negative correlation between the NPI and performance on both the second-order false belief ($r = –0.56$, $P < 0.05$) and the faux pas test ($r = –0.64$, $P < 0.05$), indicating that the degree of impairment of ToM was related to the level of neurobehavioural disturbance.

Discussion

This study is, to the best of our knowledge, the first to examine ToM performance in patients with progressive degenerative disorders, namely fvFTD and Alzheimer's disease. Patients with fvFTD were relatively mildly impaired, as judged by their ability to undertake a demanding battery of general neuropsychological tests and to cooperate fully with testing. In support of our hypothesis, patients were found to have significant deficits on the ToM tests and, although some were impaired on first- and second-order ToM (which normal children are able to perform at the ages of 3–4 and 6–7 years, respectively), a higher proportion of fvFTD patients showed deficits on the faux pas test (which children can pass between the ages of 9 and 11 years) and the Reading the Mind in the Eyes Test (which develops during adolescence). The finding of a high degree of internal consistency between the two false belief and faux pas tasks suggests that these tests may measure a common cognitive process. Patients with Alzheimer's disease, while severely amnesic, generally showed no deficits on the specific ToM-based components of the tasks.

Errors on the faux pas task revealed difficulty with several aspects of mental state inference. Some patients failed to detect when something hurtful or inappropriate had been said, indicating a lack of empathy. Some said that something inappropriate had been said when, in fact, it had not, and some inferred that something hurtful was said intentionally, indicating a failure to infer accurately the story characters' belief states. For example, one story was about a case of mistaken identity in which a customer in a restaurant orders another customer to clean up after him, thinking the person is a waiter. J.M. missed the point of mistaken identity, but explained the behaviour as, 'He did it for power, . . . he was used to ordering people about.' Thus, it may be that patients with fvFTD have deficits in several aspects of ToM.

Performance on the Reading the Mind in the Eyes Test did not correlate with any of the other ToM tests, although the patients' performance on this task was significantly poorer than that of controls. This task assesses the ability to make a judgement about the mental state of an individual solely from a photograph of the eyes, and thus may be measuring more visual aspects of mentalizing than the other ToM tasks. Alternatively, some of the words in this test are complex or abstract, such as 'hostile' or 'reflective,' and may therefore place greater demands on the semantic system than the other tests. Although patients with semantic dementia were excluded from our study, a subtle deficit was found on the Graded Naming Test, which might explain the poorer performance on the Reading the Mind in the Eyes Test. Interestingly the only positive correlation found for the Reading the Mind in the Eyes Test was with the MMSE, again perhaps implying that this test is tapping into more intellectual aspects of function rather than purely social cognition functions.

The fvFTD patients were, as a group, mildly impaired on tests of executive function, although some patients obtained scores in the normal range. Performance on the ToM tasks was, however, largely independent of the frontal measures used. Only the faux pas task correlated with one test of frontal executive function, that of WCST. Performance on the test of verbal fluency (F, A, S), which is commonly used as a screening test for frontal function, was not significantly correlated with any of the ToM tests. The finding of independence between traditional tests of frontal function and ToM is in keeping with the prior functional brain imaging findings using ToM-based tasks discussed in the Introduction.

It is also consonant with the findings of Stone *et al*. (1998) who demonstrated impairment on faux pas tasks in patients with orbitofrontal, but not dorsolateral frontal, pathology.

Analysis of the individual fvFTD patients' performance across the four ToM tasks in relation to the location, and severity, of frontal brain atrophy revealed a number of interesting findings. First, it confirmed the clear patient-by-patient correspondence between the false belief and faux pas tests and again suggested that performance on the Reading the Mind in the Eyes Test draws upon different cognitive and, presumably, neural processes. Secondly, the atrophy in fvFTD patients involved predominantly the ventromedial frontal cortex. Thirdly, there was striking concordance between the ranking of patients according to the extent of their impairment on ToM tasks and the severity of frontal lobe atrophy. The latter adds to the growing evidence in favour of a frontal substrate for ToM in humans and suggests that the ventromedial cortex might be one of the critical brain regions underlying ToM.

At present, the diagnosis of fvFTD often depends almost entirely upon relative/carer reports of change in personality and social comportment. Although instruments such as the NPI have allowed the quantification of carer-reported changes, such information is not always reliable or even available. There is clearly a need for tasks that are capable of measuring alterations in social cognition. Furthermore, although correlations between psychological tests and behavioural measures are often modest, the second-order false belief task and the faux pas task were both strongly correlated with the NPI. The faux pas task explained 41% of the variance in NPI scores, indicating that measures of ToM and social cognition may be useful clinically as an adjunct in diagnosis and for monitoring treatment responses. The findings of the study by Rahman *et al*. (1999) offer another potentially useful approach. The latter authors demonstrated that patients with fvFTD also have deficits in the complex judgements underlying performance in a gambling test and on a reversal learning test. Our ultimate goal is to develop a battery of tasks sensitive to the locus pathology found in fvFTD.

Patients with fvFTD present with a complex set of behavioural changes including loss of empathy, self-centredness, emotional coldness, stereotypic and ritualized behaviours, altered appetite and food preference, disinhibition, impulsiveness, apathy and loss of insight (Gregory and Hodges, 1996*a*, *b*; Bozeat *et al*., 2000). It is unlikely that impaired ToM underlies all these changes. Based upon the finding of severely defective ToM in autism and Asperger's syndrome, it seems likely that the symptoms of fvFTD that most clearly resemble those seen in these developmental syndromes are likely to be most closely linked to ToM. The most plausible candidate is, therefore, the impaired social awareness. Of relevance, therefore, is the recent study by Bozeat *et al*. (2000), which contrasted the neuropsychiatric and behavioural features found in fvFTD, semantic dementia and Alzheimer's disease and demonstrated distinct and discriminating clusters of symptoms. Altered social awareness with loss of empathy and disinhibition, stereotypic behaviours, mood disturbance and dysexecutive features were found to constitute four discrete symptom clusters, only the first two of which separated FTD from Alzheimer's disease. Further work is clearly required to relate the individual observable behavioural changes to the loss of ToM in FTD.

Turning to the findings in the Alzheimer's disease patient group, there was, in general, very little evidence of impairment on tests of ToM. The only task on which the Alzheimer's disease group displayed deficits was the second-order false belief test. This task places very heavy demands on working and episodic memory. It is possible that the Alzheimer's disease patients, all of whom were severely amnesic, failed this task for reasons different from those in fvFTD. The latter assumption is supported by the fact that they performed flawlessly on other tests of ToM, including the developmentally more sophisticated faux pas test and the Reading the Mind in the Eyes Test. It is also noteworthy that the Alzheimer's disease and fvFTD groups showed a double dissociation between their performance on the ToM- and non-ToM-based components of the faux pas test. Whereas Alzheimer's disease patients performed as well as controls on the detection of faux pas, they failed the 'control' memory questions. Patients with fvFTD showed the opposite pattern.

This study has a number of potential limitations. First, the controls used in this study were significantly older than the patients but, if anything, this is likely to strengthen our finding because using older control subjects would be more likely to decrease the difference between our groups. Although one study comparing college students and elderly adults found a higher ToM performance in the elderly group (Happe *et al*., 1998), a subsequent study using a wider range of age groups found that ToM declined with age (Maylor and Moulson, 2001). Moreover, we found no correlation between age and performance on ToM tasks. Analysis of covariance failed to show an effect of age and did not alter the principle findings. A second limitation is that the analysis of brain atrophy was qualitative rather than quantitative and focused on two broad regions of the frontal lobes only. Image acquisition in this cohort did not permit volumetric analysis. Furthermore, accurate parcellation of the frontal cortex presents a considerable methodological challenge. We have also not included other brain areas such as the anterior cingulate, amygdala and anterior posterior temporal regions, all of which have been implicated in processing of ToM.

From a clinical perspective, tests that are capable of quantifying changes in personality and behaviour, which are the earliest manifestation of fvFTD, may be very valuable. Measures of frontal executive function used in clinical practice, such as the WCST and verbal fluency, are relatively insensitive to the orbitofrontal pathology of fvFTD, and even sophisticated structural and functional imaging methods may

not detect changes for a number of years (Gregory *et al*., 1999). These ToM tests appear to allow an objective measurement of orbitofrontal function which seems to bear the brunt of the early pathology in fvFTD cases.

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Appendix I

Faux pas story

Jill had just moved into a new apartment. Jill went shopping and bought some new curtains for her bedroom. When she had just finished decorating the apartment her best friend Lisa came over.

Jill gave her a tour of the apartment and asked 'how do you like my bedroom?'

'Those curtains are horrible', Lisa said, 'I hope you're going to get some new ones.'

Questions

Did someone say something they shouldn't have?

If yes (clarifying questions)

Who said something they shouldn't have?

Why shouldn't they have said it?

Why do you think they did say it?

Control question

In the story, what had Jill just bought?

Non-faux pas story—control

Jim was shopping for a shirt to match his suit. The salesman showed him several shirts. Jim looked at them and finally found one that was the right colour. But when he went to the dressing room and tried it on, it didn't fit. 'I'm afraid it's too small', he said to the salesman. 'Not to worry', the salesman said. 'We'll get some in next week in a larger size.' 'Great. I'll just come back then,' Jim said.

Questions

Did someone say something they shouldn't have?

If yes (clarifying questions)

Who said something they shouldn't have?

Why shouldn't they have said it?

Why do you think they did say it?

Control question

In the story, what was Jim shopping for?