

The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia

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Abstract

Structural brain imaging and neuropsychological data implicate the orbital aspects of prefrontal cortex in the developing neuropathology of fvFTD. Damage to this region is associated with deficient performance on laboratory tasks assessing theory of mind (ToM) and affective decision-making (DM), but the relationship between these two capacities in patients with prefrontal cortex dysfunction is unclear. We studied a group of patients with early/mild fvFTD ($n = 20$) and a group of matched normal controls ($n = 10$) on the Iowa gambling task (IGT) of affective decision-making, and the “reading the mind in the eyes” (MIE) and “faux pas” (FP) tests of ToM. The fvFTD group was impaired in both ToM tasks and the IGT. While performance measures from the two ToM tasks were significantly correlated, they were not associated with IGT performance. This suggests that whilst similar prefrontal circuitry is implicated in ToM and DM tasks, these cognitive domains may be independent. In clinical settings, the IGT may be useful as a complementary tool to the frontal test battery for patients with early/mild fvFTD. Deficits in decision-making and ToM observed in this study have distinct but additive effects upon the development of social behaviour in patients with prefrontal dysfunction. © 2006 Elsevier Ltd. All rights reserved.

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1. Introduction

The frontal variant of fronto-temporal dementia (fvFTD) is a prevalent form of early onset dementia with limited techniques available for detection and treatment (Ratnavalli, Brayne, Dawson, & Hodges, 2002). Patients with fvFTD present with profound changes in aspects of social cognition that are present from early in the illness course. Common behavioural symptoms include impulsivity and socially inappropriate behaviour, lack of empathy for others, lack of insight, and impaired decision-making in daily activities. Many of these features are also seen

in patients with damage to the orbital aspect of the prefrontal cortex (Damasio, 1994; Malloy, Bihle, Duffy, & Cimino, 1993) and recent brain imaging data indicate consistent anatomical and functional abnormalities in the orbito-frontal cortex (OFC) in fvFTD patients (Diehl et al., 2004; Ibach et al., 2004; Salmon et al., 2003).

Two capacities that are critical for healthy social behaviour, theory of mind (TOM; the capacity to infer the likely thoughts and intentions of others) and decision-making, are characteristically impaired in fvFTD (Gregory et al., 2002; Lough & Hodges, 2002; Lough et al., 2006). In a similar vein, patients with orbito-frontal lesions are also bad at ToM tasks including detection of deception (Stuss, Gallup, & Alexander, 2001), faux pas (Stone, Baron-Cohen, & Knight, 1998) and cheating (Stone, Cosmides, Tooby, Kroll, & Knight, 2002). Both groups appear to lack empathy (Lough et al., 2006; Rankin, Kramer, & Miller, 2005; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003).

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Decision-making associated with differing probabilities of reward and punishment has been termed ‘affective’ decision-making. In fvFTD, Rahman and co-workers (Rahman, Sahakian, Hodges, Rogers, and Robbins (1999) demonstrated abnormal betting behaviour using the Cambridge gambling task in patients with fvFTD compared to age-matched controls. In the Iowa gambling task (IGT), a classic test of decision-making ability, OFC lesion patients persist in making choices associated with high immediate rewards but greater long-term punishments (Bechara, Damasio, Damasio, & Anderson, 1994). Their performance has been explained on the basis of impaired somatic markers as an ‘insensitivity to future rewards’ (Bechara, Damasio, & Damasio, 2000). Briefly, the somatic marker hypothesis suggests that bodily states (somatic markers), induced by emotions, come to be associated with positive or negative outcomes, and in turn influence future decision-making by reinvoking the state via the somatosensory cortex (Damasio, 1996). This is believed to increase the efficiency of decision-making by biasing the individual (overtly or covertly) toward particular outcomes.

Thus both ToM and decision-making are linked to the integrity of the orbito-frontal cortex (Bechara et al., 1994; Berthoz, Armony, Blair, & Dolan, 2002; Gregory et al., 2002; Sabbagh, Moulson, & Harkness, 2004; Stone et al., 1998). Since this region is believed to be one of the earliest sites of pathology in fvFTD (Kril & Halliday, 2004), sensitive neuropsychological measures of affective decision-making and social cognition could have clinical utility in the early detection of cognitive dysfunction in fvFTD patients.

From a neuropsychological, and indeed, anatomical perspective, the relationship between the theory of mind and decision-making remains unclear. Successful performance on the Iowa gambling task does not seem to place any demands on the ability to infer others’ beliefs and intentions. Conversely, even difficult ToM tasks may load only negligibly on decision-making systems. Nonetheless, the prefrontal mechanisms of these sets of processes appear to overlap (Bechara et al., 1994; Berthoz et al., 2002; Gregory et al., 2002; Sabbagh et al., 2004; Stone et al., 1998). One possibility is that the spatial resolution of group lesion studies is insufficient to detect anatomical dissociations between decision-making and ToM processes *within* the orbito-frontal region, an area of the brain with documented functional heterogeneity (O’Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Ongur, Ferry, & Price, 2003). Another explanation is that the extended neural circuitry involved in decision-making and ToM are distinct, and the orbito-frontal cortex simply represents the one area of convergence in two independent circuits. A further possibility is that a higher-order mechanism may regulate both affective decision-making and ToM via a common resource (Adolphs, 2003).

There were two main objectives in the present study. The first was to investigate the sensitivity of the Iowa gambling task in patients with early/mild stages of fvFTD, which has not been done previously. The second objective was to examine the relationship between deficits in affective decision-making and ToM in the same group of patients with frontal lobe degeneration. We hypothesized that performance on the decision-making and

theory of mind tasks would correlate based on a shared neural substrate in the orbito-frontal cortex.

2. Methods

2.1. Subjects

Twenty fvFTD patients were recruited as part of a broader ongoing study on fronto-temporal dementia currently being conducted at the Cognitive Neurology Division Raul Carrea Institute for Neurological Research. The present study only included patients with early/mild stages of fvFTD. All presented with prominent changes in personality plus social behaviour verified by a caregiver. They showed frontal atrophy on MRI or hypoperfusion on SPECT and there were variable deficits on tests of frontal executive function. These were compared to a group of healthy controls ($n = 10$), recruited within the same geographical area as the study patients and matched for age and level of education. FTD diagnosis was made applying Lund and Manchester criteria (Neary et al., 1998), although in keeping with studies from Cambridge we prefer the label fvFTD (Gregory et al., 2002; Rahman et al., 1999). Dementia severity was assessed using the clinical dementia severity rating scale (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982). All patients underwent a standard examination battery including neurological, neuropsychiatric and neuropsychological examinations and a MRI-SPECT.

2.2. Assessment of atrophy on MRI

To assess frontal atrophy in the fvFTD group, we used a visual rating scale developed by the Cambridge group (Galton et al., 2001; Gregory et al., 2002). The frontal ratings were undertaken using T_1 coronal images through the frontal and anterior temporal lobes. The frontal lobes were assessed, using a four-point scale (0 = no atrophy; 1 = mild atrophy; 2 = moderate; 3 = marked). Patient scans were anonymized and assessed blinded, together with scans from 10 normal age-matched control subjects by one highly experienced rater (F.M.) on two separate occasions.

2.3. General neuropsychological battery

Cognitive status was measured using the Addenbrooke’s cognitive examination (ACE) (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000) and the mini-mental state exam (Folstein, Folstein, & McHugh, 1975). Subjects were also administered a standard neuropsychological battery, in order to characterise background cognitive functioning. Premorbid IQ was assessed using the WAT-BA (word accentuation test-Buenos Aires) (Burin, Jorge, Arizaga, & Paulsen, 2000). Attention and concentration were assessed with forward digit span (Wechsler & Stone, 1987) and the trail making test (part A). Memory was assessed using the logical memory (story recall) subtest from the Wechsler memory scale-revised (Wechsler & Stone, 1987). Semantic function was assessed by the pyramid and palm trees test of associative semantic memory (Howard & Patterson, 1992), naming using the Boston naming test (adapted version) (Goodglass & Kaplan, 1983) and comprehension with the token test (adapted version) (Spreeen & Benton, 1977). Verbal fluency was tested using timed generation of words starting with the letter ‘‘P’’. Executive or frontal function was evaluated by the Raven colored progressive matrices (Raven, 1995), digit span backwards (Wechsler & Stone, 1987), the trail making test (part B) (Partington & Leiter, 1949), the letters and numbers ordering subtest from the WAIS (Wechsler & Stone, 1987) and the Wisconsin card sorting test (WCST), modified version (Nelson, 1976) and the frontal assessment battery (Dubois, Slachevsky, Litvan, & Pillon, 2000).

2.4. Decision-making task

2.4.1. Iowa gambling task

The computerised version of the Iowa gambling task involves continuous card selection from four separate decks (A, B, C and D) using a mouse, and is completed after 100 selections. Each card choice is awarded a number of points (either \$50 or \$100) but occasional choices yield an additional penalty. Card choices from decks A and B generate large wins (\$100) but occasional

heavy losses that lead to overall debt on the task. These decks are effectively ‘high risk’. Decks C and D generate smaller wins (\$50 per choice) but also smaller penalties, so that persistent selection from these decks yields a profit. These decks are ‘low risk’. The dependent variable on this task is the Net Score, calculated by subtracting the number of choices from the risky decks (A + B) from the choices from the safe decks (C + D). For the purpose of analysis, the task is divided into 5 blocks, each of 20 consecutive card choices, in order to quantify the change in decision-making across the course of the task (Bechara et al., 1994).

2.5. Theory of mind tasks

2.5.1. The mind in the eyes test

This computerized task consists of 17 photographs of the eye region of faces. The subject is required to make a choice between two words that best describe what the individual in the picture is thinking or feeling (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997).

2.5.2. Faux pas test

In this test the subject is read a story that may or may not contain a social faux pas (Stone et al., 1998). The story is placed in front of the subject so that it may be referred to as necessary, therefore reducing the demands on working memory. The subjects are shown ten stories with a faux pas and ten stories without a faux pas. After each story, the subject is asked whether something inappropriate was said and if so why. In order to understand that a faux pas has occurred, the subject has to represent two mental states. First, that the person committing the faux pas is unaware that they have said something inappropriate and, second, that the person hearing it might feel hurt or insulted. There is therefore a cognitive component, and an affective component. An additional memory question is asked to check that certain aspects of each story are retained (Lough, Gregory, & Hodges, 2001; Stone, Baron-Cohen, Calder, Keane, & Young, 2003; Gregory et al., 2002).

Performance on each component of the test was recorded separately as follows:

- Did someone say something wrong or inappropriate: 1 point for each faux pas correctly identified (correct hit), or non-faux pas correctly rejected (correct reject).
- Why should not they have said it: 1 point if they indicate *in any way* that the listener would be hurt or insulted (affective component).
- Why do you think they said it: 1 point if they *in any way* indicate that it was a mistake, or the participant did not realize what was going on (intentionality component).
- Control questions: 1 point if they correctly answered the control memory questions.

For the purpose of analysis, we recorded the number of faux pas correctly identified or rejected separately before combining them as a summed score (max. 20). The scores for the clarifying questions on correctly identified faux pas were recorded in a similar manner. A composite score was calculated which included the sum of the correctly identified (hits) and correctly rejected faux pas (rejects), together with the scores on the two faux pas clarifying questions (max. 3 points per correctly identified faux pas, max. 40 points for complete task).

2.6. Statistical analysis

Demographic and neuropsychological data were analysed using *t*-tests where appropriate. When homogeneity of variance could not be achieved even after transforming the data, a non-parametric Mann–Whitney-*U* was calculated to compare the two groups. The Iowa gambling task was analysed using a repeated measures ANOVA design with time blocks (1–5) as the within-subjects variable, and group (fvFTD or control) as the between-subjects variable. For correlation between two ordinal variables, Spearman’s rank correlation coefficient was employed. Fisher’s exact test was used instead of a χ^2 -test for measuring the independence of two categorical variables. There was one fvFTD patient who was not assessed on the faux pas task and one control who did not receive the Iowa gambling task; all other subjects received all tests. Tests were thresholded at a significance level of $P < 0.05$ using SPSS 12.0 (SPSS Inc., Chicago, IL).

Table 1
Neuropsychological performance of fvFTD patients and controls

	fvFTD (20)	NC (10)	<i>P</i>
Age (years)	67.2 (8.1)	63.5 (5.8)	ns
Sex (F/M)	9/11	6/4	ns
Education	12.8 (5.0)	13.5 (2.7)	ns
Length of history (years)	2–4		
CDR	0.62 (0.2)		
WAT-BA	34.6 (3.5)	37.1 (4.9)	ns
MMSE	27.9 (1.6)	29.5 (0.8)	0.007
ACE	85.6 (8.6)	94.8 (5.8)	0.01
Attention			
Digits forward	6.0 (1.5)	7.1 (0.9)	0.06
Trails A	65.2 (29.2)	39.7 (15.6)	0.01
Memory			
Logical memory			
Immediate	18.8 (8.3)	23.9 (8.8)	ns
Delayed	12.8 (9.0)	18.8 (9.5)	0.10
Recognition	15.2 (3.9)	17.1 (3.2)	ns
Language			
Pyramids and palm trees	49.7 (3.4)	51.8 (0.4)	0.02
Boston	18.8 (1.0)	19.8 (0.4)	0.005
Token test	22.6 (4.8)	25.1 (1.1)	0.08
Phonologic fluency	13.3 (7.1)	15.9 (4.5)	ns
Executive functions			
Raven matrices	25.7 (7.7)	30.5 (3.0)	ns
Digits backward	4.1 (1.4)	4.8 (1.0)	0.09
Trails B	123.5 (59.1)	97.7 (9.8)	ns
Letters and numbers	7.1 (2.9)	10.4 (2.4)	0.005
WCST			
Categories	3.9 (1.7)	5.3 (0.8)	0.03
Perserverative errors	9.3 (10.3)	3.8 (3.3)	ns
FAB	14.3 (4.1)	17.7 (0.5)	0.01

$P < 0.05$ is shown in bold characters. ns, not significant; CDR, clinical dementia rating scale; WAT-BA, word accentuation test-Buenos Aires; MMSE, mini-mental state examination; ACE, Addenbrooke’s cognitive examination; FAB, frontal assessment battery; WCST, Wisconsin card sorting test.

3. Results

3.1. Background neuropsychological performance and MRI data

Table 1 summarizes demographic and neuropsychological performance for fvFTD, and control groups. The groups were well matched for age ($t_{28} = 1.3$, $P = 0.2$), gender (Fisher exact test, $P = 0.70$) and education level ($U = 97.5$, $P = 0.9$).

fvFTD patients had lower scores than controls for the MMSE ($t_{28} = 2.9$, $P = 0.007$) and the ACE ($t_{28} = 2.7$, $P = 0.01$). Measures of attention and processing speed showed no difference between groups on forward digit span, but trails A performance by fvFTD patients was worse than controls ($U = 37.0$, $P = 0.01$). Analysis of logical memory scores from the Wechsler memory scale was performed with a repeated measures ANOVA (two conditions: immediate, delayed \times 2 group), which showed neither a group effect ($F(1,27) = 2.61$, $P = 0.12$), nor an interaction ($F(2,54) = 0.156$, $P = 0.9$). fvFTD group performance was worse than that of controls in both the pyramids and palms trees test ($U = 37.0$, $P = 0.02$) and the Boston naming test ($U = 38.0$,

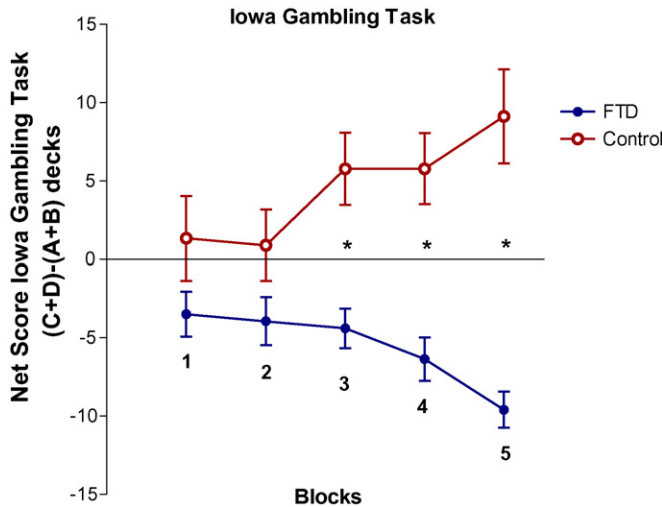


Fig. 1. Performance of fvFTD patients and controls on the Iowa gambling task, with each block (1–5) representing 20 sequential card choices. Net score is calculated by subtracting number of ‘risky’ deck selections from number of ‘good’ deck selections. A negative net score indicates poor decision-making. Circles (closed: fvFTD; open: controls) represent mean for subject groups in each block, with error bars indicating S.E.M. * $P < 0.0001$.

$P = 0.005$), but not the token test ($U = 58.0, P = 0.08$) or letter fluency ($t_{28} = 1.04, P = 0.3$).

In relation to executive measures, no significant differences were observed for: the Raven matrices ($U = 65.5, P = 0.174$), digits backwards ($U = 59.0, P = 0.09$), trails B ($t_{28} = 1.1, P = 0.3$), and perseverative errors of the WCST ($t_{28} = 1.3, P = 0.2$). fvFTD group performance was significantly lower than that of controls for letters and number ordering (WAIS) ($t_{28} = 3.1, P = 0.005$), the number of categories achieved in the WCST ($U = 52.0, P = 0.03$) and the frontal assessment battery ($U = 45.5, P = 0.01$).

MRI scans of normal controls were rated as 0 in all instances; fvFTD patients had a range of atrophy scores but none were normal (six mild, eight moderate, six marked). There was excellent intra-rater agreement (Cohen’s kappa, $\kappa = 0.8$).

3.2. The Iowa gambling task

Normal control subjects achieved an average net score (total of C + D deck choices minus A + B choices) of 22.89, indicating the development of an advantageous strategy over the course of

the task. FvFTD patients attained a mean net score of -26.5 , with repeated selection of ‘risky’ decks, particularly towards the end of the task, showing poor decision-making relative to controls (one-way ANOVA: $F(1,27) = 60.92, P < 0.0001$) (see Figs. 1 and 2). Net score from the Iowa gambling task for the two groups was normally distributed (Shapiro–Wilks): Controls (95% CI: 6.85, 38.92) and fvFTD (95% CI: $-32.60, -20.40$). This result indicates that controls preferentially chose ‘good’ blocks and that patients with fvFTD preferred ‘bad’ or ‘risky’ ones.

A repeated measures ANOVA (5-block \times 2-group) showed a marked group effect ($F(1,27) = 57.7, P < 0.0001$); fvFTD patients performed differently to controls across the 5 blocks of 20 cards each. There was also a striking block \times group interaction ($F(4,108) = 5.17, P < 0.001$). This was because although there was no significant difference in selection from decks between groups in the first two blocks, there was a marked preference in later blocks by fvFTD patients who were significantly more likely to chose cards from the risky decks (A or B). Controls preferentially chose from the ‘good’ decks (C or D) by this stage: Block 1, $F(1,27) = 3.0, P = 0.09$; Block 2, $F(1,27) = 3.1, P = 0.09$; Block 3, $F(1,27) = 17.49, P < 0.0001$; Block 4, $F(1,27) = 22.37, P < 0.0001$; Block 5, $F(1,27) = 50.68, P < 0.0001$. In effect, the two groups developed opposite strategies during the task.

3.3. Theory of mind tests

3.3.1. Mind in the eyes and faux pas tasks

Performance by patients was significantly worse than controls on the mind in the eyes task ($t_{28} = 3.65, P < 0.01$). Similarly, patients scored poorly on all measures from the faux pas task (hits: $t_{26.7} = 5.6, P < 0.001$; rejects: $t_{26.9} = 3.1, P < 0.01$; composite score: $t_{26.6} = 9.3, P < 0.001$). Table 2 shows mean scores for the fvFTD and the control group on the two ToM tasks, and Fig. 2 shows individual patient performance on the experimental tasks.

A repeated measures ANOVA (task: FP correct hits versus rejects \times group) showed a significant effect of task (i.e. identifying a faux pas correctly was harder than rejecting a non-faux pas: $F(1,27) = 30.87, P < 0.001$). There was a group effect (fvFTD performed worse than controls: $F(1,27) = 16.934, P < 0.001$) and a task by group interaction (patients were disproportionately bad at identifying when a faux pas was committed: $F(1,27) = 18.14, P < 0.001$) (see Fig. 3A).



Fig. 2. Individual patient scores on decision-making and theory of mind tasks. For the faux pas task, this represents the combined score comprising the total number of correct hits plus correct rejects.

Table 2
Theory of mind: fvFTD and control mean scores (standard deviations)

Theory of mind tests	fvFTD	Controls	<i>P</i>
“Reading the mind in the eyes test”	11.9 (2.0)	14.4 (1.4)	0.005
Faux pas test (total score)	15.0 (2.8)	19.0 (1.3)	<0.001
Hits	6.2 (2.1)	9.3 (0.9)	<0.001
Rejects	8.8 (1.0)	9.7 (0.5)	<0.01
Affective questions	3.1 (1.4)	9.0 (0.9)	<0.001
Intentionality questions	4.5 (2.1)	9.3 (0.9)	<0.001

Mean (S.D.). For faux pas test: total (max. 20); other scores (max. 10).

In order to assess whether there were differences in response between the affective and intentional components of the faux pas test, the data were analysed with a repeated measures ANOVA (task: affective versus intentional \times group). This showed a

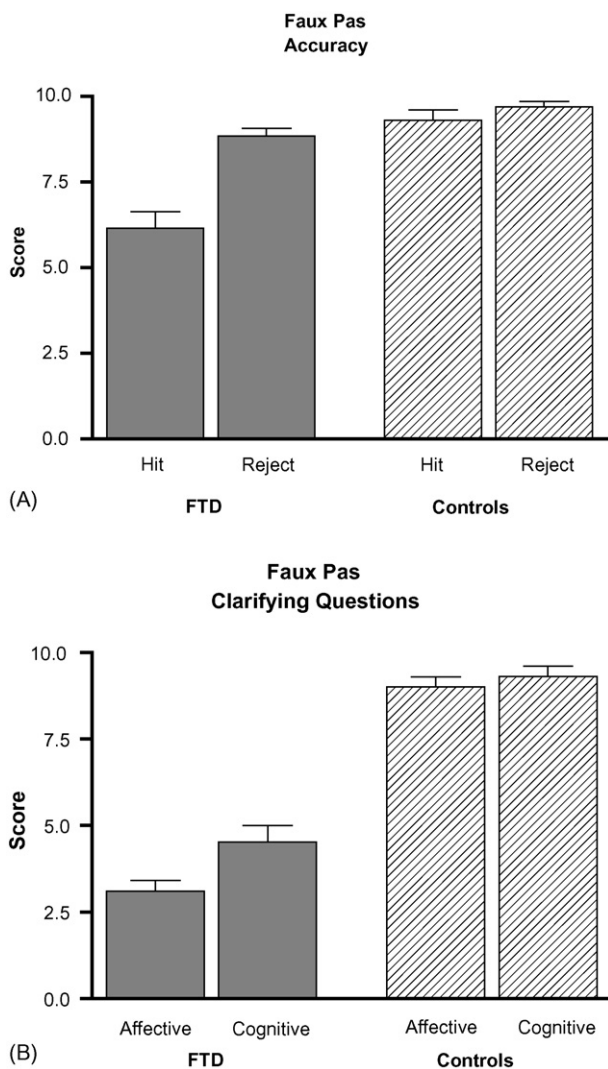


Fig. 3. (A) Performance (mean + S.E.M.) on faux pas task with scores for correctly identified faux pas and correctly rejected non-faux pas stories in fvFTD patients and controls. Patients find it harder to recognise a faux pas than controls. (B) Performance (mean + S.E.M.) on affective and cognitive (intentional) aspects of the faux pas task showing that the ability to provide an adequate mental state attribution for a faux pas in fvFTD is worse than in controls, and that affective attributions are disproportionately influenced.

strong effect of group (patients were worse than controls at both measures: $F(1,27) = 105.7$, $P < 0.001$), an effect of task (affective attributions were less likely than ‘intentional’ ones: $F(1,27) = 8.353$, $P < 0.01$) and a borderline significant interaction ($F(1,27) = 3.5$, $P = 0.07$). Post hoc testing showed that this was because FTD patients were better at providing an intentional explanation than an affective one ($t_{18} = -3.4$, $P = 0.003$) (see Fig. 3B).

The fvFTD group were then divided into two groups: a group of patients with very mild general cognitive deficits, defined as having an ACE score >88 ($n = 11$), and another group with greater impairment (ACE score <88 , $n = 9$). Those with lower ACE scores had significantly worse performance on the mind in the eyes test ($F(1,18) = 5.79$, $P = 0.027$). Performance was similar for both groups on both the faux pas and the Iowa gambling task (FP: $F(1,17) = 1.00$, $P = 0.331$; IGT: $F(1,18) = 0.014$, $P = 0.908$).

To further characterise the nature of the ToM impairments, we performed a median split on the data, dividing the group of fvFTD patients by performance on the mind in the eyes test, and secondly on their scores for the faux pas test. There were no significant differences between these groups for age, gender, level of education, ACE score, CDR or their MRI rating.

3.4. Relationship between decision-making, ToM and executive functions

Performance on the faux pas (correct hits plus rejects) was strongly correlated with mind in the eyes (MIE) scores (Pearson’s $r = 0.6$, $P = 0.007$) in fvFTD patients (see Fig. 4). These correlations remained if faux pas hits ($r = 0.5$, $P = 0.04$) or correct rejects ($r = 0.66$, $P = 0.002$) were analysed separately. The faux pas composite score (i.e. including clarifying questions) was also strongly correlated with MIE scores ($r = 0.6$, $P = 0.007$). Correlations for scores on the intentional and affective clarifying questions with MIE performance were either significant (intentionality: $r = 0.47$, $P = 0.04$) or showed a trend (affective: $r = 0.43$, $P = 0.06$).

Since we were interested in the effect of executive functions on these correlations, the analyses were repeated, controlling for the effect of performance on the WAIS letter and number sequencing task. All of the resulting partial correlations were stronger, except for the correlation between faux pas affective subscores and performance on the mind in the eyes test (faux pas hits: $r = 0.65$, $P = 0.005$; faux pas rejects: $r = 0.66$, $P = 0.003$; faux pas composite score: $r = 0.68$, $P = 0.002$; intentionality subscores: $r = 0.61$, $P = 0.009$ and affective clarifying questions: $r = 0.31$, $P = 0.23$).

Performance on the Iowa gambling task did not correlate with either ToM measure (mind in the eyes task ($r = 0.21$, $P = 0.37$)) faux pas ($r = 0.06$, $P = 0.81$) or faux pas task subscore (all $P > 0.8$); see Fig. 4.

4. Discussion

This study is, to the best of our knowledge, the first to examine the Iowa gambling task in patients with fvFTD, and to combine

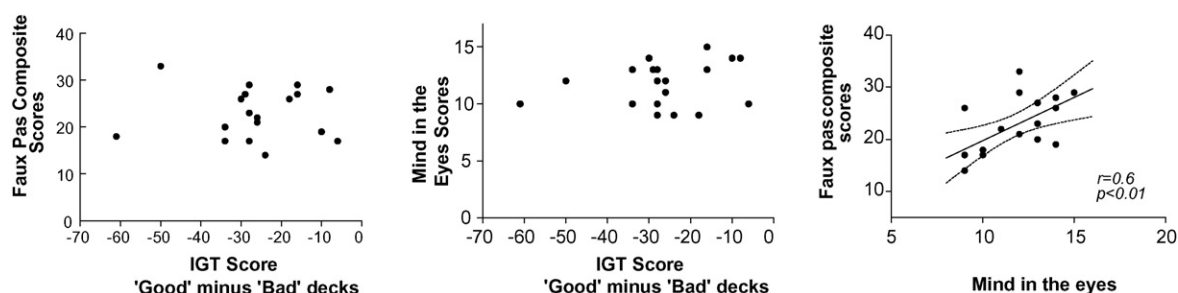


Fig. 4. Correlation between theory of mind (faux pas, mind in the eyes) and decision-making (IGT) tasks in fvFTD patients. In the correlation between the two theory of mind tasks, the 95% confidence interval is shown.

measures of ToM and decision-making in this group. We found the Iowa gambling task to be particularly sensitive to cognitive dysfunction in patients with early/mild fvFTD. There was another important finding: performance on ToM and decision-making tasks showed no association in fvFTD, while scores on the two ToM tasks were closely correlated.

4.1. The clinical importance of the Iowa gambling task in individuals with fvFTD

Decision-making is an important aspect of prefrontal function, which involves weighing up options with variable degrees of rewarding and punishing feedback. Despite the marked changes in social appropriateness, impulsivity and risk-taking in patients with fvFTD, there has been remarkably little research on this process in these patients. In this study, we observed the Iowa gambling task to be a sensitive test in early/mild fvFTD patients. The data are quite striking, with clear separation of performance between patients and controls. The groups were well matched for possible confounds such as age, gender and level of education. Furthermore, there is no subjective rating component to this task, and all participants are given identical instructions. The result is not without precedent: in 15 patients with orbito-frontal lesions, all performed disadvantageously (Bechara et al., 2000). Based on this and other previous work (Ernst et al., 2002) our result may well reflect orbito-frontal cortex dysfunction in fvFTD, although this area is unlikely to regulate decision-making in isolation: most certainly a degree of interaction with other prefrontal areas is required for optimal decision-making.

Recent studies which compare the Iowa gambling task and the Cambridge gambling task in patients with frontal damage suggest that these two tasks have differences both neuropsychologically and neuroanatomically (Clark, Manes, Antoun, Sahakian, & Robbins, 2003). Rahman et al. (1999) used the Cambridge gamble task in fvFTD patients, developed in order to assess decision-making and risk-taking behaviour outside of a learning context: relevant information is presented to subjects 'up front' and there is no need to learn or retrieve information over consecutive trials. Patients showed inflated betting behaviour, and therefore appear to be "risk-takers". The authors speculated that their results reflected ventromedial PFC dysfunction in the fvFTD patients. Experimental findings confirm the association of the Iowa gambling task with ventral PFC integrity but also highlight the importance of other prefrontal regions for this task,

including the dorsal and medial prefrontal cortex (Ernst et al., 2002; Manes et al., 2002). The Iowa gambling task also seems to have a higher demand for learning (for a review Clark & Manes, 2004).

Given the widespread prefrontal recruitment demonstrated in functional imaging studies using the Iowa gambling task (Ernst et al., 2002), and the reliance of this test on learning we suggest that in clinical usage, the Iowa gambling task may best serve as a complementary tool to a frontal test battery in the initial phases of fvFTD, before severe dementia actually develops. The effect of poor learning or impaired strategy formation in more severe cases may obscure risk-taking behaviour. Since the present study was not designed to address the specificity of the Iowa gambling task for fvFTD pathology, future studies should consider this more closely for different dementias.

4.2. Relationship between ToM and decision-making

It has been suggested that ToM is a separate cognitive module, with an innate neural basis (Happé, Brownell, & Winner, 1999), however the neural substrates of this social ability are relatively poorly understood. Although several studies have shown that patients with orbito-frontal lesions perform worse than those with dorsolateral prefrontal lesions on measures of the detection of deception, cheating, faux pas and of empathy (Shamay-Tsoory et al., 2003; Stone et al., 1998, 2002, 2003; Stuss et al., 2001), not all studies demonstrate OFC involvement in ToM tasks (Frith & Frith, 2003; Gallagher et al., 2000; Vogeley et al., 2001). Neuroimaging studies of ToM consistently identify increased activation in the medial prefrontal cortex, despite it being unclear whether lesions to this region actually impair performance (Bird, Castelli, Malik, Frith, & Husain, 2004). In the present investigation, we found no correlation between ToM and decision-making tasks in the fvFTD group despite the acknowledged involvement of the orbito-frontal cortex in both the faux pas and the Iowa gambling tasks.

One explanation for this is that the neural substrates for these two domains are actually independent. Cognitively, the development of a successful strategy on the Iowa gambling task does not require representation of the intentions or beliefs of others; likewise, ToM deficits are not clearly dependent on decision-making ability. Anatomically, this dissociation could be within the orbito-frontal region (i.e. lateral versus medial aspects). The resolution of lesion and functional imaging studies, however,

may be insufficient to dissect such anatomical heterogeneity within the OFC using these tasks.

It should also be remembered that dysfunction in fvFTD may be relatively diffuse, affecting a number of brain structures simultaneously, and that the effects are not entirely analogous to that of a focal lesion. It is believed that pathologically, fvFTD starts in superior medial and orbito-frontal regions with subsequent involvement and compromise of extended prefrontal areas (Krill & Halliday, 2004). While both decision-making and theory of mind tasks may share a neural substrate within the orbito-frontal cortex, they may be differentially affected by the extent of damage outside these regions. Interactions with areas such as the amygdala or dorsolateral prefrontal cortex, which may well be non-linear, could disproportionately bias performance on the IGT (or ToM tasks), effectively obscuring any underlying correlation related to the orbito-frontal cortex. Interestingly, we found an asymmetrical dissociation in our patient group when comparing tasks of ToM and decision-making. Deficits in decision-making can occur without deficits in ToM, but deficits in ToM usually co-occur with deficits in decision-making. Perhaps this reflects differences in task difficulty or sensitivity, or alternatively the nature of disease progression within the frontal cortex.

There was a strong correlation between the two ToM tasks in this study implying that these skills are supported by the same or similar neural substrates. The mind in the eyes test, but not faux pas was highly associated with an executive function test (WAIS letters and number ordering). When this variable was factored out in the analysis, the resulting partial correlation between the two ToM tasks was much stronger (except for the affective subscore of the faux pas test). It suggests that reading mental states from the eyes involves executive function (possibly visual working memory), which may explain some of the dorso-lateral prefrontal activation seen in functional imaging studies of this ToM task (Platek, Keenan, Gallup, & Mohamed, 2004). In general, affective scores from the faux pas correlated less well with the mind in the eyes test. A rational explanation for this would be that MIE performance requires less empathic processing than is needed for the appreciation of a faux pas. This highlights a potential dissociation between affective and intentional aspects of ToM in these tasks, and is in keeping with recent findings (Abu-Akel & Abushua'leh, 2004; Hynes, Baird, & Grafton, 2006) suggesting a relative separation of these two processes anatomically: the OFC for empathic ToM and the medial prefrontal cortex for intentional ToM. Such a dissociation may also explain earlier work in fvFTD which showed relatively preserved first and second order false belief (intentional ToM) (Gregory et al., 2002), yet markedly abnormal empathy (Lough et al., 2006). In our study, we explicitly assessed the degree of empathy engendered by the faux pas stimuli, and showed that this was more impaired in fvFTD than the ability to ascribe intention to protagonists of the faux pas.

A number of neuropsychiatric disorders which affect prefrontal cortex function are characterized by dysregulation of ToM and decision-making processes. A more subtle understanding of these complex cognitive domains will influence clinical practice in terms of improved assessment, and may allow for

the development of rational cognitive rehabilitation strategies in patients with brain injury.

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