Differential Cognitive and Affective Theory of Mind Abilities at Mild and Moderate Stages of Behavioral Variant Frontotemporal Dementia

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Objective: To study the affective and cognitive components of theory of mind (ToM) performance in patients with behavioral variant frontotemporal dementia (bvFTD), focusing on differential impairment at mild and moderate disease stages.

Background: ToM, a central capacity for appropriate social behavior, is critically impaired in patients with bvFTD, even early in the disease. No previous study has explored how the cognitive and affective components of ToM may relate differentially to disease severity.

Methods: We assessed 40 patients with an established diagnosis of bvFTD and 18 healthy controls, using a complete neuropsychological battery that featured executive function and ToM tasks. We used patients' Clinical Dementia Rating scores to classify them as having either mild or moderate bvFTD.

Results: Both groups of patients showed deficits in the affective and cognitive components of ToM relative to the controls. The patients with mild bvFTD outperformed the group with moderate bvFTD in cognitive ToM capacities; however, affective ToM was equally impaired in both bvFTD groups. The cognitive, but not the affective, component of ToM correlated with performance on the executive function tests.

Conclusions: Our results suggest that affective ToM is markedly diminished even during the initial stages of bvFTD; as the disease progresses, deficits in cognitive ToM become more prominent. These findings may relate to the pattern of cortical atrophy described for bvFTD. We also found significant correlations between the cognitive component of ToM and executive functions.

Key Words: behavioral variant frontotemporal dementia, theory of mind, executive functions, social cognition, frontal lobes

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ACE-R = Addenbrooke Cognitive Examination–Revised. **bvFTD** = behavioral variant frontotemporal dementia. **CDR** = Clinical Dementia Rating. **IFS** = INECO (Institute of Cognitive Neurology) Frontal Screening. **MMSE** = Mini-Mental State Examination. **PFC** = prefrontal cortex. **ToM** = theory of mind. **WCST** = Wisconsin Card Sorting Test.

Behavioral variant frontotemporal dementia (bvFTD) is a neurodegenerative disease that causes profound changes in patients' behavior and personality, associated with progressive frontal and anterior temporal lobe atrophy (Seeley et al, 2008). Behavioral changes may include disinhibition, social inappropriateness, compulsions, loss of insight, loss of empathy, excessive jocularity, and gluttonous overeating. These changes generally appear in the earlier stages of the disease, usually preceding the onset of cognitive deficits, and tend to be best recognized by the patient's closest relatives, friends, and colleagues.

Among the cognitive deficits are impaired executive functions and decision making (eg, as measured by the Iowa Gambling Task), deficits in theory of mind (ToM) (eg, Faux Pas Recognition Test and Reading the Mind in the Eyes test), and inhibitory control (eg, Hayling Test). These deficits are thought to reflect initial orbitofrontal cortex degeneration that begins during the early stages of the disease (eg, Hornberger et al, 2008; Torralva et al, 2009a). Some authors (Ibañez and Manes, 2012) have interpreted the emergence of these deficits in the light of an underlying impairment in the contextual integration of multiple social clues in different cognitive domains.

ToM, an essential capacity for appropriate social behavior, is critically impaired in patients with bvFTD

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(Eslinger et al, 2007; Funkiewiez et al, 2012; Gleichgerrcht et al, 2011; Gregory et al, 2002; Lough et al, 2006; Poletti et al, 2012; Snowden et al, 2003; Torralva et al, 2007, 2009a). ToM is the ability to attribute mental states to others and to predict, describe, and explain others' behavior on the basis of those mental states (Baron-Cohen et al, 1997; Poletti et al, 2012). ToM has been described as a multidimensional construct comprising both a cognitive and an affective component (Shamay-Tsoory et al, 2009, 2010). Cognitive ToM is the ability to process inferences about others' beliefs and intentions; affective ToM is the ability to process other people's emotions and feelings.

Recent studies have revealed a distributed network underlying these abilities, including the neuroanatomic complex formed by the posterior superior temporal sulcus, the adjacent temporoparietal junction area, the precuneus, and the prefrontal cortex (PFC) (Carrington and Bailey, 2009; Poletti et al, 2012). Lesion studies have shown the key role of the PFC in ToM abilities (Roca et al, 2011; Rowe et al, 2001; Stuss et al, 2001).

In 2005 and 2007, Shamay-Tsoory showed that performance on affective tasks is impaired mainly when the ventromedial PFC is damaged, but not when lesions affect other areas of the PFC. Thus, the ventromedial PFC plays a major role in affective ToM, rather than ToM abilities in general. This finding has been further supported by a neuroimaging study (Sebastian et al, 2012) showing greater ventromedial PFC activation during an affective ToM task than during a cognitive one.

The neural basis of the cognitive component of ToM is far less established (Poletti et al, 2012). Kalbe et al (2010) provided evidence of an important role of the dorsolateral PFC in cognitive ToM tasks, and Xi et al (2011) showed that patients with dorsolateral PFC lesions had a specific impairment in the cognitive component of the Faux Pas Test, ie, incorrect inferences about other people's mental states.

Impaired ToM typically underlies the unusual social behavior of patients with bvFTD. Almost all group studies of bvFTD have found a shared severe deficit in both the cognitive and affective components of ToM abilities (Eslinger et al, 2007; Gleichgerrcht et al, 2011; Snowden et al, 2003; Torralva et al, 2007, 2009a, 2009b). Still, no study to date has explored the association between ToM deficits and disease stage by looking differentially at the cognitive and affective components of ToM.

This led us to investigate ToM abilities in patients with bvFTD across different stages of the disease. We hypothesized that in the early stages, when more selective involvement of the ventromedial PFC is expected (Broe et al, 2003), the affective component of ToM would be particularly affected. In contrast, in the moderate stages, as more widespread degeneration of PFC circuits is expected, patients would evidence a more general ToM deficit that included both cognitive and affective components. To seek out the underpinnings of the cognitive impairment in this process, we further tested whether these 2 ToM components could be related to general or distinct tests of executive functions.

METHODS

We adapted parts of our methods from previous studies by our group (Roca et al, 2014; Torralva et al, 2009a). The design was approved and supervised by the ethics committee at the Institute of Cognitive Neurology (INECO) in Buenos Aires, Argentina. All participants gave their informed consent during the initial interview.

Participants

Patients with bvFTD were recruited through referrals to the INECO, which is a major center for FTD in Buenos Aires, Argentina. The patients were recruited as part of a broader ongoing study of FTD. For this study, we evaluated 40 patients in the mild and moderate stages of bvFTD who met consensus criteria for "probable bvFTD" (Rascovsky et al, 2011).

The patients presented with prominent changes in personality and social behavior, verified by a caregiver. We used the Clinical Dementia Rating (CDR) Scale to assess the severity of their dementia (Hughes et al, 1982). Two experts on FTD (author F.F.M. and neurologist Noelia Pontello) made the diagnosis of the patients' bvFTD. Inter-rater agreement for the diagnosis was excellent (Cohen kappa = 0.91).

We tested the patients with a standard battery of neurologic, neuropsychiatric, and neuropsychological assessments that included classic executive function tests and ToM tests, and we performed magnetic resonance imaging or single photon emission computed tomography. All the patients who had magnetic resonance scans showed frontal atrophy, and all those who had single photon emission computed tomograms showed frontal hypoperfusion. Although current criteria do not require abnormal imaging findings for a diagnosis of bvFTD, our study included only patients who had frontal atrophy. We also excluded patients who met the diagnostic criteria for any psychiatric disorder.

We compared our patients' test performance to that of 18 healthy controls matched to the patients for age, sex, and level of education. We recruited the controls from the same geographic area as the patients, through an announcement on INECO's website as well as with posters and word of mouth. We interviewed the volunteers before enrolling them and excluded those who met the diagnostic criteria for any neurologic or psychiatric disorder.

We assessed the controls with the same cognitive battery as the patients. A trained neuropsychologist (author T.T.) performed the cognitive assessments for all participants over 2 sessions at INECO.

Cognitive Assessment

General Neuropsychological Battery

To measure cognitive status, we used the Addenbrooke Cognitive Examination–Revised Version (ACE-R) (Mioshi et al, 2006) and the Mini-Mental State Examination (MMSE) (Folstein et al, 1975). The ACE-R is a well-validated scale that has proved useful for the assessment of patients with dementia.

Executive Function Tests

INECO Frontal Screening (Torralva et al, 2009b). This is a brief, sensitive, and specific tool for the detection of early executive dysfunction. The screen includes 8 subtests: motor programming, interference, go–no go, digit span backward, months, spatial working memory, proverbs, and verbal inhibitory control test.

Digit Span Backward (Wechsler, 2007). Participants are presented with digits in series increasing from 2 to 8 in length, and are asked immediately to speak the numbers back to the examiner in reverse order. This task assesses mental manipulation and verbal working memory.

Verbal Fluency (Benton and Hamsher, 1976). In this test, participants are asked to say as many words as possible beginning with the letter *P* during 1 minute. The objective is to assess spontaneous production of words beginning with a given letter in a limited period of time.

Trail Making Test Parts A and B (Partington and Leiter, 1949). In Part A, participants are given a pencil and a sheet of paper with the numbers 1 through 25 randomly arranged on it; they are asked to connect the numbers in ascending sequence without lifting the pencil. In Part B, they are given another sheet of paper that has both numbers and letters (a total of 25 characters), and are asked to connect them in an alternating ascending sequence (1, A, 2, B, and so forth), again without lifting the pencil. Both parts of the test are timed in seconds. These tests were designed to assess speed of attention, sequencing, mental flexibility, visual search, and set shifting. To obtain the most specific measure of our participants' cognitive flexibility, we subtracted their Part A score from their Part B score.

Modified Wisconsin Card Sorting Test. We used Nelson's modification of the Wisconsin Card Sorting Test (WCST) (Nelson, 1976), which uses 2 sets of 24 cards and eliminates ambiguity by removing those cards that share >1 attribute with the stimulus cards. This test, which measures abstraction ability and the capacity to shift cognitive strategies, is considered a gold standard of the classic tests of executive functions.

ToM Tests

Reading the Mind in the Eyes Test (Baron-Cohen et al, 1997). We used a computerized Argentinean version, in which participants are shown 17 photographs of the eye region of different human faces. The participants have to choose which 1 of 2 adjectives best describes what the individual in the picture is thinking or feeling.

Faux Pas Recognition Test of Cognitive and Affective ToM (Stone et al, 1998). We gave the participants a validated Spanish-language version of the Faux Pas Test to assess their cognitive and affective ToM. In this test, the examiner reads aloud to each participant a total of 20 brief stories. A written version of each story is also placed in front of the participants to ensure that they can retain the most important information from each story in their working memory (Lough et al, 2001). In half of the stories, someone commits a social faux pas, unintentionally

TABLE 1. Demographic Data and Neuropsychological Test Results for Controls and the 2 Patient Groups with Behavioral Variant Frontotemporal Dementia (bvFTD)

		Patients with bvFTD		Controls	Controls	Mild bvFTD
	Controls (n = 18)	Mild (n = 26)	Moderate (n = 14)	Versus Mild bvFTD	Versus Moderate bvFTD	Versus Moderate bvFTD
Demographic data						
Age (years)	64.5 (6.4)	65.8 (7)	69.9 (8.5)	ns	ns	ns
Men:women	7:11	11:15	7:7	ns	ns	ns
Education (years)	14.08 (2.7)	15.08 (4.6)	14.8 (5.7)	ns	ns	ns
Cognitive status						
Mini-Mental State Examination[1]	29.2 (1.0)	25.4 (5)	20.3 (4.3)	**< 0.01**	**< 0.01**	**< 0.01**
Addenbrooke Cognitive Examination–Revised[2]	95.3 (5.9)	78.0 (13.9)	56.2 (19.2)	**< 0.01**	**< 0.01**	**< 0.01**
Executive function						
INECO Frontal Screening[3]	27.4 (1.3)	15.8 (7.1)	9.6 (6.3)	**< 0.01**	**< 0.01**	**< 0.05**
Wisconsin Card Sorting Test[4]	5.5 (0.7)	2.5 (2.7)	1 (0.77)	**< 0.01**	**< 0.01**	**< 0.01**
Digits Backward[5]	4.8 (1.1)	3.5 (1.5)	2.5 (0.7)	**< 0.01**	**< 0.01**	**< 0.05**
Verbal fluency[6]	17.7 (5.3)	10.12 (4.8)	6.4 (3.9)	**< 0.01**	**< 0.01**	**< 0.05**
Trail Making Test Part B minus A (seconds)[7]	55 (36)	137 (93)	249 (42)	**< 0.01**	**< 0.01**	**< 0.01**

Other than ratios, values are shown as mean (standard deviation).
[1]Folstein et al, 1975. [2]Mioshi et al, 2006. [3]Torralva et al, 2009b.[4]Nelson, 1976.[5]Wechsler, 2007. [6]Benton and Hamsher, 1976. [7]Partington and Leiter, 1949.
INECO = Institute of Cognitive Neurology. **ns** = not significant.

TABLE 2. Theory of Mind: Comparison of Mean Scores for the Controls and 2 Patient Groups with Behavioral Variant Frontotemporal Dementia (bvFTD)

	Controls (n = 18)	Patients with bvFTD		Controls Versus Mild bvFTD	Controls Versus Moderate bvFTD	Mild bvFTD Versus Moderate bvFTD
		Mild (n = 26)	Moderate (n = 14)			
Reading the Mind in the Eyes Test[1]	14.5 (1.4)	8.7 (3.4)	8.2 (2.8)	**< 0.01**	**< 0.01**	0.60
Faux Pas Recognition Test[2]						
Total	18.7 (1.2)	13.6 (3.7)	9.0 (3.5)	**< 0.01**	**< 0.01**	**< 0.01**
Hits	9.3 (0.6)	5.9 (3.2)	3.2 (2.6)	**< 0.01**	**< 0.01**	**< 0.01**
Rejects	9.4 (0.7)	8.08 (2.3)	5.7 (2.9)	**< 0.01**	**< 0.01**	**< 0.01**
Cognitive component	8.13 (2.2)	5.6 (2.5)	2.1 (2.2)	**< 0.01**	**< 0.01**	**< 0.01**
Affective component	7.6 (1.7)	3.5 (2.9)	2.0 (1.7)	**< 0.01**	**< 0.01**	0.09

Values are shown as mean (standard deviation).
Bold type indicates statistical significance at $P < 0.05$.
[1]Baron-Cohen et al, 1997. [2]Stone et al, 1998.

saying something hurtful or offensive to another person. In the other half of the stories, no faux pas is committed. The score is calculated as the total number of stories accurately identified as containing a faux pas ("hits") and as not containing a faux pas ("rejects").

When participants correctly identify a faux pas, the examiner asks them 2 additional questions. The first concerns intentionality—the ability to recognize that the person committing the faux pas was not aware that he or she had said something inappropriate (maximum score = 10). The second question concerns emotional attribution—the ability to recognize that the person hearing the faux pas might have felt hurt or offended (maximum score = 10) (Roca et al, 2014). The first question measures cognitive ToM; the second, affective ToM. In addition to these follow-up questions, the examiner gave the participants control questions that we did not use in the analysis.

Statistical Analysis

We analyzed performance for our 3 groups: the 18 healthy controls, 26 patients with mild bvFTD and a CDR score of 1 point, and 14 patients with moderate bvFTD and a CDR score of 2 points. We compared demographic and neuropsychological data for the 3 groups using a 1-way analysis of variance design, with Tukey honest significant difference post hoc comparisons when appropriate. When analyzing categorical variables (eg, sex), we used the Freeman-Halton extension of the Fisher exact probability test for 2 × 3 contingency tables.

RESULTS

Neuropsychological Profile

Table 1 lists general demographic information and neuropsychological test results for the controls and 2 patient groups.

Patients and controls were successfully matched for age ($t_{56} = 0.07$, $P = 0.12$), sex ($\chi^2 = 0.93$, $df = 1$, $P = 0.40$), and years of education ($t_{55} = 0.9$, $P = 0.74$). We found significant differences for ACE-R scores among the 3 groups ($F_{2,55} = 32.7$, $P < 0.001$). This difference was significant between the patients with mild and those with moderate bvFTD ($P < 0.001$), between controls and patients with mild bvFTD ($P < 0.001$), and between controls and patients with moderate bvFTD ($P < 0.001$).

We observed a similar pattern with the MMSE ($F_{2,55} = 25.3$, $P < 0.001$), with the controls differing significantly from both the patients with mild bvFTD ($P < 0.001$) and those with moderate bvFTD ($t_{30} = -8.3$, $P < 0.001$). The 2 groups of patients also differed significantly from each other ($P = 0.001$).

All 5 executive function measures differed between groups: total score of the INECO Frontal Screening (IFS) ($F_{2,52} = 35.6$, $P < 0.001$); total categories score of the WCST ($F_{2,50} = 41.2$, $P < 0.001$); Trail Making Test Part B minus Part A performance ($F_{2,51} = 35.7$, $P < 0.001$); digit span backward ($F_{2,53} = 13.3$, $P < 0.001$); and verbal fluency scores ($F_{2,54} = 23.8$, $P < 0.001$). We found significant differences between the controls and the patients with mild bvFTD on all 5 of these executive measures (all Ps < 0.01). We also found significant differences between the controls and the patients with moderate bvFTD in the same measures (all Ps < 0.01). Finally, we observed post hoc significant differences between the 2 bvFTD groups on all of the executive function tests (all Ps < 0.05), with the patients with mild bvFTD outperforming those with moderate bvFTD.

ToM Tests

Reading the Mind in the Eyes and Faux Pas Recognition Tests

Performance on the Reading the Mind in the Eyes test differed significantly among the 3 groups ($F_{2,53} = 37.6$, $P < 0.001$). We found differences between the controls and the patients with mild bvFTD ($P < 0.001$) and those with moderate bvFTD ($P < 0.001$).

TABLE 3. Theory of Mind: Mean and Median Scores for the Controls and 2 Patient Groups with Behavioral Variant Frontotemporal Dementia (bvFTD)

	Controls (n = 18)		Patients with Mild bvFTD (n = 26)		Patients with Moderate bvFTD (n = 14)	
	Mean (Standard Deviation)	Median (Range)	Mean (Standard Deviation)	Median (Range)	Mean (Standard Deviation)	Median (Range)
Reading the Mind in the Eyes Test[1]	14.5 (1.4)	15 (12-17)	8.7 (3.4)	7 (4-14)	8.2 (2.8)	8.5 (4-15)
Faux Pas Recognition Test[2]						
Total	18.7 (1.2)	19 (17-20)	13.6 (3.7)	14 (5-10)	9 (3.5)	9 (4-17)
Hits	9.3 (0.6)	9 (8-10)	5.9 (3.2)	7 (0-10)	3.2 (2.6)	3 (0-9)
Rejects	9.4 (0.7)	10 (8-10)	8.08 (2.3)	9 (3-10)	5.7 (2.9)	4 (2-10)
Cognitive component	8.13 (2.2)	8 (4-9)	5.6 (2.5)	6 (0-10)	2.1 (2.2)	2 (0-8)
Affective component	7.6 (1.7)	8 (3-10)	3.5 (2.9)	3 (0-10)	2 (1.7)	2 (0-6)

[1]Baron-Cohen et al, 1997. [2]Stone et al, 1998.

There were no significant differences between the 2 groups of patients ($P = 0.96$).

Performance on the Faux Pas Test showed the same pattern ($F_{2,54} = 38.7$, $P < 0.001$). Similarly, both groups of patients scored poorly on all measures of the Faux Pas Test: hits ($F_{2,54} = 23.4$, $P < 0.001$); rejects ($F_{2,54} = 11.6$, $P < 0.001$); cognitive score ($F_{2,52} = 28.8$, $P < 0.001$); and affective score ($F_{2,52} = 23.5$, $P < 0.001$). We also found significant differences between the controls and the patients with mild bvFTD in all Faux Pas measures: total Faux Pas ($P < 0.001$), hits ($P < 0.001$), rejects ($P < 0.01$), cognitive score ($P < 0.001$), and affective score ($P < 0.001$). We also found post hoc significant differences between the controls and the patients with moderate bvFTD on the same measures (all Ps < 0.01). The 2 bvFTD (mild versus moderate) groups differed significantly on the Faux Pas scores, hits, rejects, and cognitive score (all Ps < 0.01), with the patients with mild bvFTD outperforming those with moderate bvFTD. Affective scores did not differ significantly between the patient groups ($P = 0.12$).

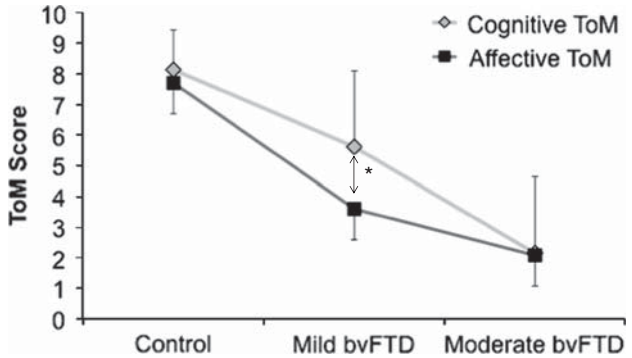

FIGURE 1. Cognitive and affective theory of mind (ToM) test scores for 18 healthy controls, 26 patients with mild behavioral variant frontotemporal dementia (bvFTD), and 14 patients with moderate bvFTD. The patients with mild bvFTD had significantly lower affective than cognitive ToM scores.

Table 2 compares mean scores for the 3 groups on the ToM tasks, and Figure 1 shows the groups' cognitive and affective ToM values. Table 3 shows medians and ranges for the ToM scores. Importantly, when we introduced the MMSE as a covariate in the analysis, we saw the same effects.

Relationship Between ToM and Executive Functions

For this analysis, we evaluated all the patients with bvFTD as a single group. As shown in Table 4, the patients' total performance on the Faux Pas Test (measured as correct hits plus correct rejects) correlated strongly with both their MMSE and ACE-R scores. Their performance also correlated significantly with all the executive function measures: WCST, Trail Making Test Part B minus Part A, IFS, verbal fluency, and digit span backward.

The affective component of the Faux Pas Test showed no correlations with any executive function test. However, the cognitive component correlated positively with the WCST and the IFS.

We found no correlations between the patients' total Reading the Mind in the Eyes scores and any measure of cognition, or with the Faux Pas Test.

DISCUSSION

This study is the first to examine the differential involvement of distinct ToM abilities in patients at different stages of bvFTD. We assessed 40 patients with an established diagnosis of bvFTD using a neuropsychological battery that included tests of cognitive function and ToM. Based on their CDR scores, we classified the patients as being in either the mild or moderate stage of the disease. We demonstrated that, even though patients with bvFTD have impaired overall performance in ToM, its affective component is distinctly affected in the mild stages of the disease, while deficits in the cognitive component become more marked only as the disease progresses to a moderate stage. Both of our patient

TABLE 4. Correlation Coefficients and Associated *P* Values Between Theory of Mind and Cognitive and Executive Functions for the 40 Patients with Behavioral Variant Frontotemporal Dementia

	Mini-Mental State Exam[1]	Addenbrooke Cognitive Exam–Revised[2]	Wisconsin Card Sorting Test[3]	Trail Making Test[4] Part B minus Part A	INECO Frontal Screening[5]	Verbal Fluency[6]	Digits Backward[7]
Reading the Mind in the Eyes Test[8]							
r	−0.17	−0.23	0.10	−0.27	0.01	−0.5	0.12
P	0.27	0.15	0.56	0.12	0.99	0.75	0.44
Faux Pas Recognition Test[9] (total)							
r	0.53	0.56	0.53	−0.49	0.67	0.58	0.5
P	**< 0.011**	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**
Cognitive component							
r	0.30	0.30	0.36	−0.26	0.35	0.25	0.31
P	0.6	0.06	**0.03**	0.13	**0.03**	0.12	0.55
Affective component							
r	0.22	0.30	0.31	−0.26	0.30	0.27	0.10
P	0.16	0.06	0.06	0.13	0.06	0.08	0.54

Bold type indicates statistical significance at $P < 0.05$.
[1]Folstein et al, 1975. [2] Mioshi et al, 2006. [3]Nelson, 1976. [4]Partington and Leiter, 1949. [5]Torralva et al, 2009b. [6]Benton and Hamsher, 1976. [7]Wechsler, 2007. [8]Baron-Cohen et al, 1997. [9]Stone et al, 1998.
INECO = Institute of Cognitive Neurology.

groups showed deficits in the affective and cognitive components of ToM relative to controls; the patients with mild bvFTD outperformed the group with moderate bvFTD in cognitive but not affective ToM.

Our results are consistent with previous reports suggesting that the social impairments of patients with bvFTD may be related to their ToM deficits, which tend to be evident even in the early stages and to progress over time (Adenzato et al, 2010; Eslinger et al, 2007; Gleichgerrcht et al, 2011; Poletti et al, 2012; Snowden et al, 2003; Torralva et al, 2007, 2009a). The complex neuroanatomic network underlying ToM abilities includes the posterior superior temporal sulcus, the adjacent temporoparietal junction areas, the precuneus, and, chiefly, the PFC (Carrington and Bailey, 2009; Roca et al, 2011). This network largely overlaps with the areas involved in bvFTD. Accordingly, mesial and orbital frontal regions have been reported to be the earliest structures affected by the neuronal degeneration in bvFTD, followed by the anterior temporal pole and dorsolateral frontal cortices, and eventually the hippocampal formation and the basal ganglia (Kril and Halliday, 2004).

This pattern of progressive degeneration among patients with bvFTD can therefore differentially involve distinctive components of ToM. As we demonstrated in this study, patients with early bvFTD present with a profound impairment of affective ToM and a milder deficit in cognitive ToM, and their deficit in cognitive ToM appears to worsen as their disease advances. This specific directionality is expected in view of converging evidence (Sebastian et al, 2012; Shamay-Tsoory et al, 2005, 2007) that performance on affective ToM tasks is impaired mainly when lesions damage the ventromedial PFC, but not when they affect other areas of the PFC (Poletti et al, 2012). Evidently, the ventromedial PFC is essential for affective ToM in particular.

Our results are in line with studies published by Roca and collaborators (2010, 2014) demonstrating the exact opposite pattern in a group of patients with mild relapsing-remitting multiple sclerosis and a group with Parkinson disease. In both studies, the authors showed that the earlier involvement of the dorsolateral PFC in these diseases, with relative sparing of the ventromedial PFC in the early stages, impairs cognitive but not affective ToM. Taken together, these studies and our present results can shed light on the relationship between cognitive and affective ToM and their link with different neural circuits within the PFC.

The cognitive profile of patients with bvFTD is usually characterized by deficits in executive function and generation of words, with relative sparing of visuospatial functions (Perry and Hodges, 2000; Rascovsky and Grossman, 2013). Because traditional neuropsychological tests often fail to capture early changes in bvFTD, new tools are being developed aimed at measuring the orbitofrontal and ventromedial integrity of the frontal lobes. Our results suggest that sensitive measures of the affective component of ToM might help enable earlier diagnosis of bvFTD.

Findings in ToM and executive function have not been without controversy, however. Studies have demonstrated correlations between ToM measures and executive functions, making it difficult to attribute deficits in ToM tasks to a selective deficit in mentalizing (Eslinger et al, 2007; Torralva et al, 2007). In the present study, we found significant correlations between total Faux Pas scores (cognitive and affective ToM combined) and measures of cognitive (MMSE and ACE-R) and executive functions (IFS, WCST, Trail Making Test Part B minus Part A, and

digit span backward); however, we found no correlation at all between the Reading the Mind in the Eyes test and any of the cognitive measures included in our neuropsychological battery. Furthermore, after dividing the Faux Pas Test into its cognitive and affective components, we found no association between the affective component and any executive function test. On the contrary, and as expected based on our current findings, the cognitive component of the Faux Pas Test correlated significantly with some measures of executive function (IFS and WCST).

Although the results are controversial, a great number of studies have shown dissociations between performance on ToM tasks and traditional executive tests (eg, Gregory et al, 2002; Roca et al, 2010, 2014). In our present study, the cognitive component of the Faux Pas Test was evidently related to some extent to executive performance, suggesting that the ability to infer what others are thinking requires functions such as working memory, abstraction capacity, and flexibility. Loss of the ability to infer others' thoughts may be associated with the degeneration of the dorsolateral PFC found in patients with bvFTD and with activation of the dorsolateral PFC reported in imaging studies using the Faux Pas Test (Kalbe et al, 2010; Xi et al, 2011).

The present study had some limitations. First, as in most clinical studies, our diagnosis of bvFTD was based on clinical assessment alone, without pathologic confirmation. Long-term follow-up of our patients will allow for postmortem analysis. However, the new criteria for bvFTD (Rascovsky et al, 2011) provide more diagnostic certainty by distinguishing between possible and probable bvFTD. All of our patients fulfilled the criteria for probable bvFTD.

Second, use of the CDR as a dementia-staging tool in patients with FTD has now been superseded by the Frontotemporal Dementia Functional Rating scale (Mioshi et al, 2010), which was developed specifically as a tool to stage FTD, and bvFTD in particular. Further studies should replicate our findings using this newer tool.

A third consideration concerns our analyses. We cannot judge whether our patients' performance on the Reading the Mind in the Eyes test was merely random (given the group's average nearing 50% accuracy) or just markedly impaired. Further, we did not correct our correlation analyses for multiple comparisons. These questions could be clarified by using the complete version of the Reading the Mind in the Eyes test, which gives 4 choices of descriptive adjectives in each trial, rather than the 2 adjectives that we used. We encourage further replications of our study with alternative versions of this task.

Finally, even though researchers often use patients' cognitive and functional status as a measure of FTD progression and then derive neuroanatomic hypotheses, future studies should analyze the differential involvement of specific frontal regions and derive more precise measures of disease progression. Then we would be able to study the status of different ToM abilities at different disease stages using neuroanatomic criteria.

In summary, while previous studies have shown that patients with bvFTD have a deficit in ToM involving both its affective and cognitive components, our study further demonstrates that cognitive and affective ToM are differentially affected, with cognitive ToM being relatively spared in the early stages. This difference reflects the patterns of atrophy and progression characteristic of bvFTD. Further research is needed to establish the exact nature of affective and cognitive deficits and their impact on patients' everyday living. In this regard, even if we can infer that the cognitive deficits observed in clinical settings are linked to the functional and social impairments of patients with bvFTD, future studies will need to address more directly the impact that affective ToM deficits have on patients' real life impairments.

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REFERENCES

Adenzato M, Cavallo M, Enrici I. 2010. Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. *Neuropsychologia*. 48:2–12.

Baron-Cohen S, Jolliffe T, Mortimire C, et al. 1997. Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger Syndrome. *J Child Psychol Psychiatry*. 38:813–822.

Benton AL, Hamsher K. 1976. *Multilingual Aphasia Examination*. Iowa City, Iowa: University of Iowa Press.

Broe M, Hodges JR, Schofield E, et al. 2003. Staging disease severity in pathologically confirmed cases of frontotemporal dementia. *Neurology*. 60:1005–1011.

Carrington SJ, Bailey AJ. 2009. Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Hum Brain Mapp*. 30:2313–2335.

Eslinger PJ, Moore P, Troiani V, et al. 2007. Oops! Resolving social dilemmas in frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 78:457–460.

Folstein MF, Folstein SE, McHugh PR. 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the physician. *J Psychiatr Res*. 12:189–198.

Funkiewiez A, Bertoux M, de Souza LC, et al. 2012. The SEA (Social cognition and Emotional Assessment): a clinical neuropsychological tool for early diagnosis of frontal variant of frontotemporal lobar degeneration. *Neuropsychology*. 26:81–90.

Gleichgerrcht E, Torralva T, Roca M, et al. 2011. The role of social cognition in moral judgment in frontotemporal dementia. *Soc Neurosci*. 6:113–122.

Gregory CA, Lough S, Stone V, et al. 2002. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain*. 125:752–764.

Hornberger M, Piguet O, Kipps C, et al. 2008. Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology*. 71:1481–1488.

Hughes CP, Berg L, Danziger WL, et al. 1982. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 140:566–572.

Ibañez A, Manes F. 2012. Contextual social cognition and the behavioural variant of frontotemporal dementia. *Neurology*. 78:1354–1362.

Kalbe E, Schlegel M, Sack AT, et al. 2010. Dissociating cognitive from affective theory of mind: a TMS study. *Cortex*. 46:769–780.

Kril JJ, Halliday GM. 2004. Clinicopathological staging of frontotemporal dementia severity: correlation with regional atrophy. *Dement Geriatr Cogn Disord*. 17:311–315.

Lough S, Gregory C, Hodges JR. 2001. Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. *Neurocase*. 7:123–130.
Lough S, Kipps CM, Treise C, et al. 2006. Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*. 44:950–958.
Mioshi E, Dawson K, Mitchell J, et al. 2006. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry*. 21:1078–1085.
Mioshi E, Hsieh S, Savage S, et al. 2010. Clinical staging and disease progression in frontotemporal dementia. *Neurology*. 74:1591–1597.
Nelson H. 1976. A modified card sorting response sensitive to frontal lobe defects. *Cortex*. 12:313–324.
Partington JE, Leiter RG. 1949. Partington's pathways test. *Psychol Serv Bull*. 1:9–20.
Perry RJ, Hodges JR. 2000. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. *Neurology*. 54:2277–2284.
Poletti M, Enrici I, Adenzato M. 2012. Cognitive and affective Theory of Mind in neurodegenerative diseases: neuropsychological, neuroanatomical and neurochemical levels. *Neurosci Biobehav Rev*. 36:2147–2164.
Rascovsky K, Grossman M. 2013. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. *Int Rev Psychiatry*. 25:145–158.
Rascovsky K, Hodges JR, Knopman D, et al. 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 134(pt 9):2456–2477.
Roca M, Manes F, Gleichgerrcht E, et al. 2014. Cognitive but not affective theory of mind deficits in mild relapsing-remitting multiple sclerosis. *Cogn Behav Neurol*. 27:25–30.
Roca M, Torralva T, Gleichgerrcht E, et al. 2010. Impairments in social cognition in early medicated and unmedicated Parkinson disease. *Cogn Behav Neurol*. 23:152–158.
Roca M, Torralva T, Gleichgerrcht E, et al. 2011. The role of Area 10 (BA10) in human multitasking and in social cognition: a lesion study. *Neuropsychologia*. 49:3525–3531.
Rowe AD, Bullock PR, Polkey CE, et al. 2001. 'Theory of mind' impairments and their relationship to executive functioning following frontal lobe excisions. *Brain*. 124:600–616.
Sebastian CL, Fontaine NM, Bird G, et al. 2012. Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Soc Cogn Affect Neurosci*. 7:53–63.
Seeley WW, Crawford R, Rascovsky K, et al. 2008. Frontal paralimbic network atrophy in very mild behavioural variant frontotemporal dementia. *Arch Neurol*. 65:249–255.
Shamay-Tsoory SG, Aharon-Peretz J. 2007. Dissociable prefrontal networks for cognitive and affective theory of mind: a lesion study. *Neuropsychologia*. 45:3054–3067.
Shamay-Tsoory S, Harari H, Szepsenwol O, et al. 2009. Neuropsychological evidence of impaired cognitive empathy in euthymic bipolar disorder. *J Neuropsychiatry Clin Neurosci*. 21:59–67.
Shamay-Tsoory S, Onur OA, Kessler J. 2010. Dissociating cognitive from affective theory of mind: a TMS study. *Cortex*. 46:769–780.
Shamay-Tsoory SG, Tomer R, Berger BD, et al. 2005. Impaired "affective theory of mind" is associated with right ventromedial prefrontal damage. *Cogn Behav Neurol*. 18:55–67.
Snowden JS, Gibbons ZC, Blackshaw A, et al. 2003. Social cognition in frontotemporal dementia and Huntington's disease. *Neuropsychologia*. 41:688–701.
Stone VE, Cohen SB, Knight RT. 1998. Frontal lobe contribution to theory of mind. *J Cogn Neurosci*. 10:640–656.
Stuss DT, Gallup GG, Alexander MP. 2001. The frontal lobes are necessary for 'theory of mind'. *Brain*. 124:279–286.
Torralva T, Kipps CM, Hodges JR, et al. 2007. The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia. *Neuropsychologia*. 45:342–349.
Torralva T, Roca M, Gleichgerrcht E, et al. 2009a. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain*. 132: 1299–1309.
Torralva T, Roca M, Gleichgerrcht E, et al. 2009b. INECO Frontal Screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia. *J Int Neuropsychol Soc*. 15:777–786.
Wechsler D. 2007. *Wechsler Adult Intelligent Scale III*, 3rd ed. San Antonio, Texas: The Psychological Corporation.
Xi C, Zhu Y, Niu C, et al. 2011. Contributions of subregions of the prefrontal cortex to the theory of mind and decision making. *Behav Brain Res*. 221:587–593.