Social Mind Representation: Where Does It Fail in Frontotemporal Dementia?

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Abstract

■ We aimed at investigating social disability and its cerebral correlates in frontotemporal dementia (FTD). To do so, we contrasted answers of patients with early-stage FTD and of their relatives on personality trait judgment and on behavior prediction in social and emotional situations. Such contrasts were compared to control contrasts calculated with answers of matched controls tested with their relatives. In addition, brain metabolism was measured in patients with positron emission tomography and the [^{18}F]fluorodeoxyglucose method. Patients turned out to be as accurate as controls in describing their relative's personality, but they failed to predict their relative's behavior in social and emotional circumstances. Concerning the self, patients were impaired both in current personality assessment and in prediction of their own behavior. Those two self-evaluation measures did not correlate. Only patients' anosognosia for social behavioral disability was found to be related to decreased metabolic activity in the left temporal pole. Such results suggest that anosognosia for social disability in FTD originates in impaired processing of emotional autobiographical information, leading to a self-representation that does not match current behavior. Moreover, we propose that perspective-taking disability participates in anosognosia, preventing patients from correcting their inaccurate self-representation based on their relative's perspective. ■

INTRODUCTION

Frontotemporal dementia (FTD) is characterized by prominent alteration of personal and social judgment. Behavioral changes frequently occur before cognitive impairments and they remain the major symptoms of the frontal variant of the disease (fvFTD) (Pasquier, Lebert, Lavenu, & Guillaume, 1999). Core diagnostic features of fvFTD include early decline in social interpersonal conduct, early impairment in the regulation of personal conduct, early emotional blunting, and early loss of insight (Neary et al., 1998). In the neuropathological domain, predominant frontal and/or anterior temporal atrophy has been identified, but the relative distribution of lesions is heterogeneous (Jackson & Lowe, 1996; Constantinidis, Richard, & Tissot, 1974). In keeping with pathological observations, functional imaging studies show variance in both the extent and localization of impaired brain activity in FTD (Garraux et al., 1999; Starkstein et al., 1994). Accordingly, a conjunction analysis on a large sample of metabolic images obtained in patients with FTD from different European centers demonstrated consistent involvement of a limited number of brain regions principally located in the rostral limbic complex (Salmon et al., 2003).

Despite a well-developed set of criteria describing the symptoms of FTD, the disease remains difficult to diagnose in the early stages. The core diagnostic features for fvFTD seem to rely mainly on a social dimension, as betrayed by personality changes and attitudes toward rule-breaking behaviors. However, no unified theory explaining pathological behavior in FTD has been proposed, nor is there any standardized evaluation of patients' social dysfunction.

Social disability in FTD is associated with emotional processing and mind representation deficits (Lough et al., 2005; Rosen et al., 2004; Gregory et al., 2002; Keane, Calder, Hodges, & Young, 2002; Lough, Gregory, & Hodges, 2001; Perry et al., 2001; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999). Mind representation (i.e., theory of mind [ToM]), also referred to as mentalizing, empathy, or perspective taking, is the ability to attribute intentions, thoughts, and feelings to oneself and others (Frith & Frith, 1999). It allows one to interpret and understand other people's actions and speech and predict their behavior. Neuropsychological investigations have demonstrated that ToM impairment is related to cortical lesions located in the dorsolateral prefrontal cortex, the orbital prefrontal cortex, the temporal pole, or the temporoparietal junction (Apperly, Samson, Chiavarino, & Humphreys, 2004; Samson, Apperly, Chiavarino, & Humphreys, 2004; Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Happe,

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Brownell, & Winner, 1999; Eslinger, 1998; Stone, Baron-Cohen, & Knight, 1998). Functional neuroimaging studies of healthy subjects have given congruent results, because attributing thoughts to others reliably activated the medial prefrontal cortex, the temporal poles, especially in the left hemisphere, and the temporoparietal junction, especially in the right hemisphere (Frith & Frith, 2003). Several neuroimaging studies have demonstrated that self-related thoughts also recruited part or all of this network (D'Argembeau et al., 2005; Lou et al., 2004; Ochsner et al., 2004). The shared neurophysiological correlates between self- and other processing are hypothesized to originate in a common coding system for self- and other representation (Ruby & Decety, 2001, 2003). It has been suggested that the temporoparietal junction and the medial frontopolar cortex underlie the mechanism that distinguishes between the self and others, allowing one to attribute an action or thought to its proper agent (Ruby & Decety, 2004). Interestingly, when patients with FTD were required to assess a character's preference according to gaze direction, Snowden et al. (2003) found that ToM impairment was associated with an increased egocentric bias in third-person perspective taking (i.e., in incorrect answers, patients with FTD tended to give their own preference, irrespective of the character's gaze direction). One possible explanation is that patients with FTD fail to overcome the confusion induced by the common coding system due to their significant ventromedial prefrontal dysfunction, which prevents them from suppressing self-thoughts (Samson, Apperly, Kathirgamanathan, & Humphreys, 2005; Ruby & Decety, 2004).

In summary, FTD appears to be a disease that impairs both emotional processing (emotional blunting) and mind representation, whether of other people's minds (TOM impairment) or one's own mind (loss of insight into behavioral disturbances). Ruby and Decety (2004) demonstrated that perspective taking with social emotion in healthy subjects activates the ventromedial prefrontal cortex and the temporal pole, both of which are damaged in patients with FTD. Hence, perspective-taking assessment in a social and emotional context was expected to be an efficient tool for detecting and measuring social impairments in fvFTD from the onset of the disease.

In this study, we used both a procedure for perspective taking in social and emotional situations (Ruby & Decety, 2004) and a standardized personality judgment procedure (Klein, Rozendal, & Cosmides, 2002) to explore social mind representation and quantify social disability in FTD. Most previous studies that have investigated FTD used reports by the patient's relatives to assess personality changes (Rankin, Kramer, Mychack, & Miller, 2003; Perry et al., 2001; Miller et al., 1997). The patient's report was usually considered as unreliable. However, patients' answers constitute an open window on the psychopathological processes taking place in FTD. Collecting reports from both parties allowed us to compare these subjective perspectives directly and then to assess not only personality disturbances, but also a number of psychological parameters such as perspective-taking ability, egocentric bias in perspective taking, and anosognosia. Finally, we wanted to explore the neural substrate of social disability in fvFTD by using clinicometabolic correlations between behavioral measures assessing social mind representation and brain metabolism estimated at rest with positron emission tomography and the [^{18}F]fluorodeoxyglucose method (FDG-PET). We predicted that patients with FTD would demonstrate first- and third-person perspective impairment when compared with control subjects matched for age and level of education. We further hypothesized that patients with FTD would demonstrate an increased egocentric bias in third-person perspective taking compared with healthy subjects (i.e., an abnormal similarity between the patient's first- and third-person perspectives). Finally, impaired perspective-taking ability in fvFTD was predicted to correlate with metabolic impairments in the rostral limbic complex.

METHODS

Subjects

Patients with fvFTD (13 men and 8 women) were selected according to recent consensual diagnostic criteria (Neary et al., 1998). Mean age was 64 ± 9 years (range, 48–80 years). Mean education level was 11 ± 4 years, and mean disease duration was 42 ± 26 months. Mean score on the Dementia Rating Scale (Mattis, 1976) was 127 ± 11 over 144. For the behavioral study, 16 patients (10 men and 6 women) were matched one by one, as closely as possible, with controls according to age, education, and relationship with the relative who also took part in the testing (see Supplementary Table 1). Mean age was 66 ± 7 years for this group of patients and their controls, and mean education level was 11 ± 4 years for patients and 12 ± 4 years for controls. Five patients from this group did not undergo functional imaging investigation. Consequently, five additional patients (and their relatives) were added to the initial population in order to run a correlation analysis between behavioral testing and brain metabolism at rest in a group of 16 patients (see Supplementary Table 1). Neither significant cerebral vascular lesions nor extreme atrophy were observed after visual inspection of the anatomical imaging in these early-stage fvFTD cases. The study was approved by the local ethics committee of the University of Liège. Informed consent was obtained from all subjects included in the study (patients, relatives, and healthy controls), in accordance with the Helsinki declaration.

Experimental Procedure

Two groups were tested. The patient group consisted of 16 couples (dyads) made up of a patient and a close relative. The control group comprised 16 couples made up of control subjects, each matched for age, sex, and education to one patient, and a close relative. The term "subject" (S) will be used to refer to patients and their matched control subjects, and (R) refers to all of the relatives.

Each subject was presented with two questionnaires, one concerning behavior prediction and one for personality assessment. For all subjects, behavior prediction was presented before personality assessment, and the order of presentation of the various questions was always the same. Questionnaires were read to the subjects by the experimenter. A choice of possible answers was presented after each question. Subjects indicated their answers orally. The entire testing session lasted around one and a half hours.

Perspective Taking in Social Situations

The behavior prediction questionnaire was composed of 60 sentences describing real-life situations likely to induce emotional reactions (e.g., "You are late for an appointment, how do you react?"; for more details, see Ruby & Decety, 2004). Subjects were instructed to indicate how they would probably react in such a situation by choosing one of three proposed adjectives. Subjects were presented with distinct triads of adjectives describing emotional reactions, depending on the situation depicted in the sentence ("shocked/indifferent/sympathetic"; "panicked/bothered/calm"; "angry/upset/resigned," "suspicious/carefree/excited"; "impressed/proud/detached"; "irritated/embarrassed/relaxed").

In the first-person perspective condition, subjects (S) and their relatives (R) were instructed to answer questions taking a first-person perspective (S1, R1), that is, to indicate the reaction they would have if they faced such a situation. The subjects were also asked to indicate how they thought they would have reacted 10 years before (S1bef).

In the third-person perspective condition, subjects and relatives were instructed to answer questions taking a third-person perspective (S3, R3), that is, to indicate the reaction they thought their relative would have in such a situation, or "to put themselves in their relative's shoes." The subjects' relatives also had to say how they thought the subjects would have reacted 10 years before and, more specifically, before the onset of dementia in the case of the subjects with FTD (R3bef).

The aim of this procedure was to obtain two subjective perspectives (first- and third-person) on the behavior of one individual (subject or relative) in a given situation. The responses of the group comprising patients and their relatives and the group of healthy control subjects with their relatives were compared. Subjects answered conditions in the following order: S1, S1bef, and S3 for the patients and their control subjects, and R1, R3, and R3bef for all the relatives.

Assessment of Own and Relative's Personality

The personality assessment questionnaire comprised 60 adjectives describing personality traits that were close to previously obtained norm means on the dimensions of meaningfulness and familiarity (Kirby & Gardner, 1972; Anderson, 1968) and spanned the range of social desirability (Klein et al., 2002). Subjects were instructed to indicate how well the adjective described their own or their relative's personality by choosing a number from 1 to 4 (1 = *not at all*; 2 = *a little*; 3 = *quite well*; 4 = *totally*).

In the self-assessment condition, subjects and relatives were instructed to answer how well the adjective described their own personality (S1, R1). The subjects (S) were also asked to answer how well the adjective described their personality 10 years before (S1bef).

In the "other" assessment condition, subjects and relatives were instructed to answer how well the adjective described their relative's personality (S2, R2). The subject's relative was also instructed to answer how well the adjective described the subject's personality 10 years ago and, more specifically, before the dementia started in the case of the FTD subjects (R2bef). Subjects answered conditions in the following order: S1, S1bef, and S2 for the patients and controls, and R1, R2, and R2bef for the relatives.

Note that, in both questionnaires, subjects were asked to describe their relatives. However, the perspective taken by the subjects for this description was different in the two conditions. Subjects made a first-person perspective judgment of their relative's personality (S2), whereas they took a third-person perspective (S3) to answer how their relative would react in a socioemotional situation.

Behavioral Measures

Scores for the discrepancy between patient and caregiver have been previously used to assess patients' reliability in own personality assessment (Tulving, 1993) and anosognosia in Alzheimer's disease (Salmon et al., 2006; Kalbe et al., 2005; Migliorelli et al., 1995). Such a methodology (comparing self and other on various judgments to highlight abilities and inabilities in self and social knowledge) was first introduced into mainstream neuropsychological literature by Klein and colleagues, who widely used it to assess knowledge of self in control populations and in patients (Klein, Cosmides, & Costabile, 2003; Klein et al., 2002; Klein, Loftus, & Kihlstrom, 1996). In our study, for both questionnaires, answers in the different conditions were compared (within or between subjects) to obtain discrepancy scores, which were expressed as a percentage of divergent answers over the total number of answers. The discrepancy scores were not normally distributed (according to the Kolmogorov–Smirnov test). Consequently, Mann–Whitney *U* tests were used to compare median discrepancy scores in the patient and control groups (the statistical threshold was set at $p < .005$, taking multiple comparisons into account).

The discrepancy scores calculated were as follows (S = subject, R = relative): Egocentricity (S1–S3 and S1–S2) measures the difference that subjects think there is between their own behavior/personality and that of their relatives. A decrease in this score indicates an increased egocentric bias, that is, a tendency to attribute own thoughts/traits to the other person.

The third-person perspective-taking ability (S3–R1) measures subjects' ability to predict their relatives' emotional reactions in a social situation.

The accuracy of assessment of the relatives' personality (S2–R1) measures subjects' accuracy in judging their relatives' personality.

The behavioral (R3–R3bef) and personality (R2–R2bef) change, as assessed by the relative, measure perceived changes over 10 years in the subject's social behavior and personality.

Anosognosia for behavioral (S1–R3) and personality (S1–R2) change measure subjects' lack of awareness of their current social behavior or personality. We are aware of the difficulty to interpret a discrepancy score measured with two subjective perspectives as reflecting anosognosia, but in the precise context of dementia, previous studies suggest that an inadequate report of the patient is more likely than erroneous assessment of the relative (Salmon et al., 2006).

Reliance on past behavior (S1–R3bef) or past personality (S1–R2bef) measure the extent to which subjects see themselves as they were 10 years before or, more accurately, as their relatives remember them being 10 years before. These scores measure the influence of memories of own past personality or behavior on current self-personality assessment and social behavior prediction.

Current behavioral (R1–R3) and personality (R1–R2) congruence with the relative measure current social behavior or personality congruence (or difference) between the relative and the subject, according to the relative.

Previous behavioral (R1–R3bef) and personality (R1–R2bef) congruence with the relative measure the difference between the relatives' current social behavior or personality and the subject's social behavior or personality 10 years before, as assessed by the relatives.

Self-assessment of behavioral or personality change (S1bef–S1) measures the difference between current and past personality or social behavior, according to the subject.

Neuropsychological Testing

All patients underwent a short neuropsychological "executive" evaluation comprising the Stroop test (Stroop, 1935), the Brixton test (Burgess & Shallice, 1996), and phonological and semantic fluency tasks (Cardebat, Doyon, Puel, Goulet, & Joanette, 1990). These tasks assess, respectively, inhibitory processes, the ability to detect rules in sequences of stimuli, and the ability to apply an organized strategy to search for information in long-term memory.

The Stroop task consists of a naming condition (to name the color of colored patches), a reading condition (to read the names of colors printed in black), and an interference condition (saying what color a word is when it is printed in an incongruent ink color, e.g., the word *red* printed in green). The measure of inhibition is the increase in response latencies between the naming and interference conditions.

The Brixton text consists of a series of pages presented one at a time to participants. Each page features 10 circles numbered 1 to 10, the only difference between pages being the position of the filled-in circle. The subject's task is to predict which circle will be filled in on the next page. The correct position could be determined based on the position on the current page by a simple rule, which changes after from three to eight pages. The number of errors made by participants is scored.

In the verbal fluency tasks, participants were given 120 sec to generate aloud a list of words belonging to a specific semantic category (semantic fluency task, category of animals) or beginning with a target letter (phonemic fluency task, letter *P*) but excluding proper names and variants of the same word. The number of words generated (without errors and repetitions) was recorded.

Subscores of the Dementia Rating Scale (Mattis, 1976), such as "concept formation" and "memory," were also used for correlation with scores derived from the questionnaires.

PET Acquisition

PET images were acquired in patients on a Siemens (Erlangen, Germany) CTI 951 R 16/31 scanner during quiet wakefulness with eyes closed and ears unplugged after an intravenous injection of 110 to 370 MBq [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG). Images of tracer distribution in the brain were used for analysis: Scan starting time was 30 min after tracer injection and scan duration was 20 min. Images were reconstructed using filtered backprojection including correction for measured attenuation and scatter using standard software.

PET scans were not available for five patients with FTD in the initial population. Hence, five additional couples were added to the group of patients in order to perform a clinicometabolic correlation analysis. For these five couples, a limited procedure was applied and only S1, S3/S2 and R1, R3/R2 conditions were collected for both questionnaires. Their age, disease duration, level of education, and total score on the Mattis test did not significantly differ from those of the other patients (Mann–Whitney U test, $p > .05$). The median for the delay between the FDG-PET scan and testing in the patients with FTD was 82 days, with a range from 6 to 318 days (the latter in a very stable patient).

PET Image Processing

SPM 2000 (SPM2) routines (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks Inc., Natick, MA) were used to perform basic image processing and voxel-based statistical analysis. All PET scans were checked and spatially normalized by nonlinear and affine 12-parameter transformation to the SPM2 standard brain template. Images were then smoothed with a 12-mm full width at half maximum isotropic kernel filter. Areas of significant metabolic change between the two populations (patients with FTD and matched controls) were estimated according to a general linear model using linear contrasts. Global activity adjustment was performed using proportional scaling.

In a first analysis, groups were made up of 16 subjects with FTD and 16 age-matched controls from our normal database. Statistical analysis in SPM consisted of a condition and covariate design with two conditions (FTD and controls). A simple comparison procedure was performed to contrast metabolism in patients and controls. The threshold of significance was set at $p_{(\text{uncorrected})} < .0005$. In a second step, we explored the neural correlates of mind representation in FTD by performing behavioral–metabolic correlation analyses in the patient group. We used the discrepancy scores measuring anosognosia for behavioral changes and perspective-taking disability in patients [(S1–R3) and (S3–R1)] and their equivalents in the questionnaire of personality assessment measuring anosognosia for personality changes and decreased accuracy of judgment for other's personality assessment [(S1–R2) and (S2–R1)]. Age was entered as confounding covariate. The correlated set of voxels was thresholded at $p_{(\text{corrected})} < .05$. Brain coordinates for SPM results corresponded to the Montreal Neurological Institute (MNI) standard space. Note that impaired metabolism in fvFTD was considered to originate from both regional atrophy and decreased brain activity, and metabolism was not corrected for brain atrophy in this study.

RESULTS

Questionnaire of Behavior Prediction

The statistical analysis revealed significant differences between patient and control groups on several, but not all discrepancy scores, as illustrated in Figure 1. Supple-

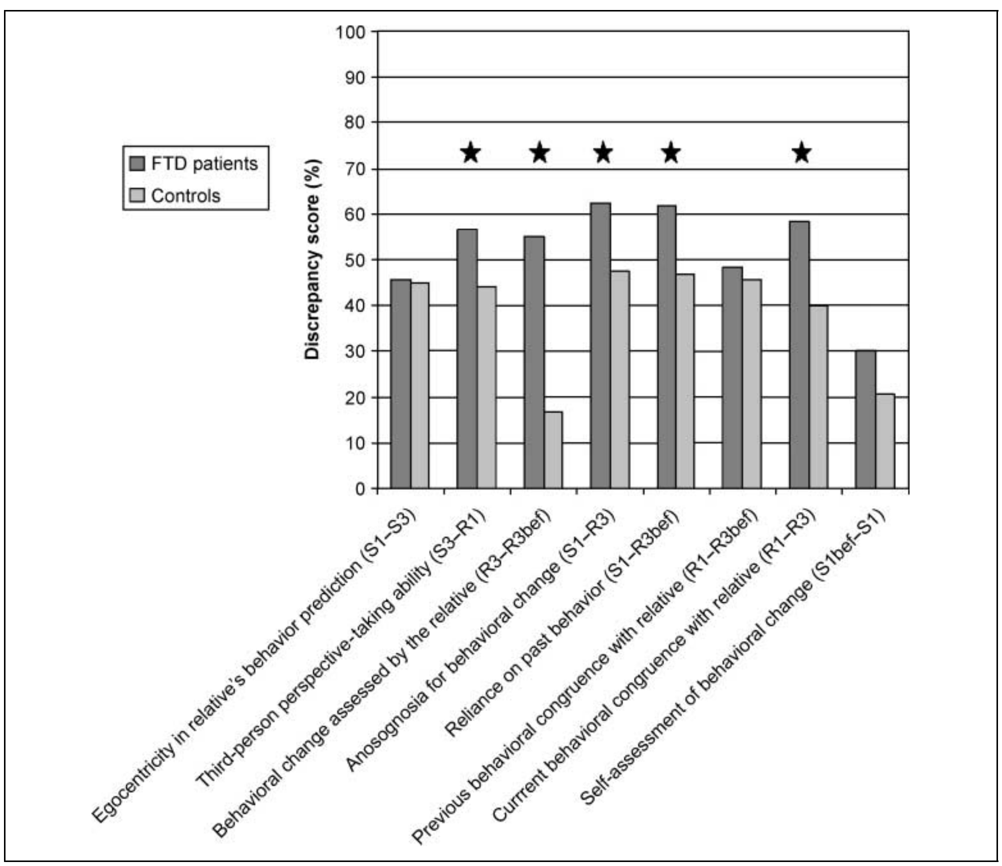


Figure 1. Median discrepancy score for the behavior prediction questionnaire in the patients with FTD and in the control subjects. Significant differences between groups are indicated with a star ($p < .005$).

mentary Table 2 presents the ranges of discrepancy scores. According to their relatives, the patients' reactions had changed a lot in the last 10 years, whereas such changes were not reported for the control group (R3–R3bef). The congruence between the subject's previous behavior and the relative's current behavior (as assessed by the relatives) was not significantly different in the patient and the control group (R1–R3bef), whereas the congruence between the subject's and the relative's current behaviors (as assessed by the relatives) was significantly lower in the patient group than in the control group (R1–R3).

The high anosognosia score (S1–R3) for the patient group revealed that patients tended to be unaware of their behavioral changes. The personal impression of change (S1bef–S1) revealed two pieces of clinical information. On the one hand, patients felt that they had not changed a lot in the past 10 years. On the other hand, they were consistent in their self-evaluation during a single session (although their evaluation was inaccurate). The score for reliance upon previous behavior (S1–R3bef) suggested that the patients' first-person perspective was not based on accurate memories of their behavior before the dementia set in, because their current self-evaluation differed from their relatives' assessment of their behavior 10 years ago. The egocentricity score (S1–S3) did not differ between the groups, highlighting the patients' preserved ability to distinguish between self and other, as they predicted different reactions for themselves and their relatives when facing the same social situation. Finally, patients with FTD made more perspective-taking mistakes than did controls when assessing their relatives' emotional reaction (S3–R1).

Personality Assessment Questionnaire

The statistical analysis revealed significant differences between patient and control groups on several scores, as illustrated in Figure 2 and Supplementary Table 3.

According to their relatives, patients had changed more than controls in the last 10 years (R2–R2bef). The congruence between the subject's previous personality and the relative's current personality (as assessed by the relatives) was not significantly different in the patient and the control group (R1–R2bef), whereas the congruence between the subject's and the relative's current personality (as assessed by the relatives) was significantly lower in the patient group than in the control group (R1–R2).

The significantly higher anosognosia score (S1–R2) in the patient group revealed that patients with FTD and their relatives strongly disagreed about the patients' current personality; that is, that patients were not very aware of their personality changes. The personal impression of change (S1bef–S1) showed that patients felt that they had not changed much in the past 10 years.

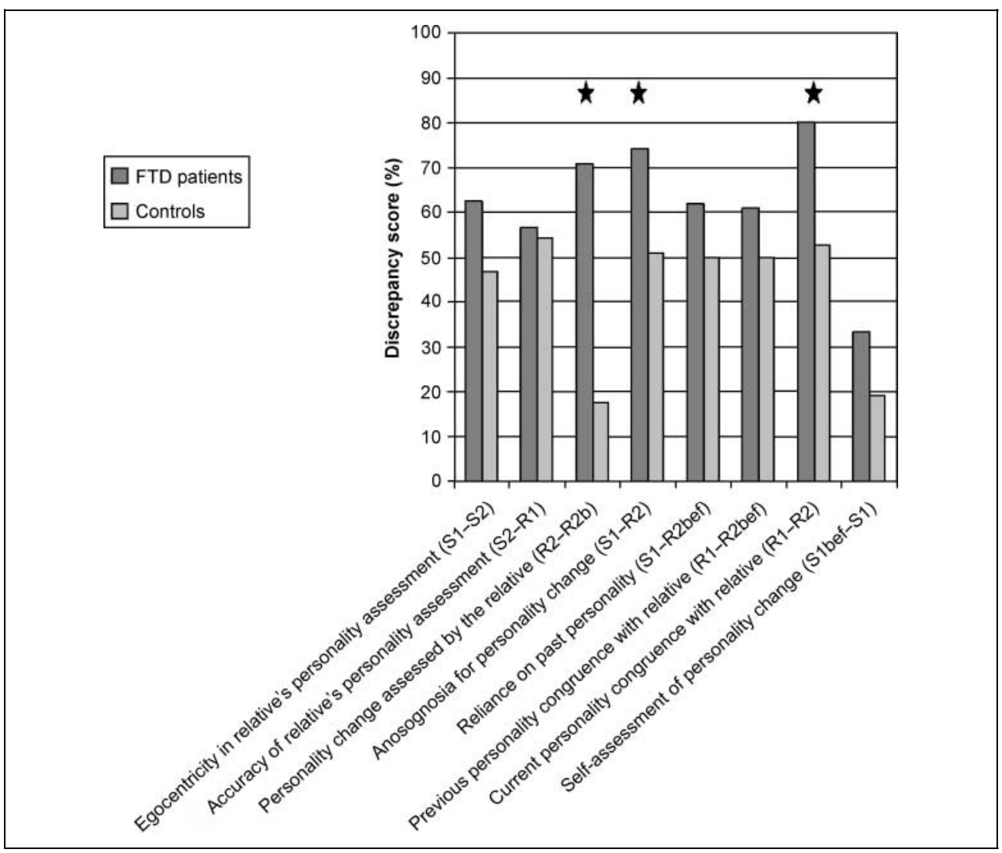


Figure 2. Median discrepancy score for the personality assessment questionnaire in the patients with FTD and in the control subjects. Significant differences between groups are indicated with a star ($p < .005$).

Moreover, the relative similarity between the answers demonstrated that subjects with FTD were consistent in their responses during the same session. Unlike the results for the behavior prediction questionnaire, patients' assessments of their current personality fitted with their relatives' assessments of the patients' personality 10 years ago (S1–R2bef), suggesting that the patients were relying on old memories of their personality traits, which they had failed to update since the onset of the dementia. Patients with FTD had a preserved capacity to differentiate between themselves and others in terms of personality assessment according to the egocentricity score (S1–S2). The patients also appeared to have a preserved ability to assess their relatives' personality (S2–R1).

Correlations between Discrepancy Scores and Neuropsychological Performance

The Spearman test was used to search for correlations between the discrepancy scores reflecting perspective taking (S3–R1), anosognosia (S1–R3 and S1–R2), and accuracy of judgment of the relative's personality traits (S2–R1), and the neuropsychological results, in order to test for putative dependency between the scores and executive or language abilities. Neuropsychological performance consisted of total errors during the interference condition in the Stroop test (9.6 ± 9.8; range, 0–37) and interference index (.36 ± .12; range, .09–.60), semantic fluency (18 ± 5 words in 2 min, range from 7 to 24) and phonological fluency (14 ± 6 words in 2 min; range, 2–25), number of correct answers for the Brixton test (28 ± 7, range, 17–34), memory performance (21 ± 4; range, 10–25), concept understanding (35 ± 4; range, 25–39), and total score on the Dementia Rating Scale (128 ± 12; range, 99–140). No significant correlation was found between discrepancy scores and the cognitive performance measured in the study, or between the two discrepancy scores assessing anosognosia (S1–R3 and S1–R2) ($p < .0025$, using Bonferroni correction).

Regional Reduction in Metabolism in Patients with FTD Compared with Age-matched Controls

The patients had been clinically diagnosed and selected as fvFTD (Neary et al., 1998). Consistent with previous reports (Salmon et al., 2003), impaired metabolism was detected in the orbitofrontal cortex and the subgenual area, in different regions of the lateral prefrontal cortex, and in the left anterior temporal lobe (Table 1 and Figure 3).

Correlation between Behavioral and Metabolic Data

Two correlation matrices were designed in SPM by using FDG-PET scan and the discrepancy scores assessing social mind representation. In the first analysis, judgment accuracy for the relative's personality traits (S2–R1) and anosognosia score concerning personality (S1–R2) were included in a design matrix with age as confounding variable. Age was taken as a confounding covariate because it is known to influence medial prefrontal activity (Martin, Friston, Colebatch, & Frackowiak, 1991). We did not find any correlation between discrepancy scores concerning personality traits and cerebral metabolism.

Next, scores for perspective taking (S3–R1) and anosognosia concerning social reactions (S1–R3) were included in a second design matrix with age as confounding variable. No significant correlation was found between the discrepancy score reflecting impaired perspective taking (S3–R1) and resting brain FDG uptake in patients with FTD. The anosognosia score (S1–R3), an index of unawareness of own social behavior, was found to be inversely correlated with brain activity in the superior part of the left temporal pole ($x = -40$, $y = 12$, $z = -20$; $p_{(corrected)} < .05$, Z score = 4.97; cluster extent = 315 voxels; see Figure 4). At a lower significance level ($p < .001$, uncorrected), the anosognosia score was also correlated with glucose metabolism in the inferior part of the left temporal pole ($x = -58$, $y = -10$, $z = -30$; Z score = 3.75) and in the superior part of the right temporal pole ($x = 56$, $y = 18$, $z = -14$; Z score = 4.35). The less aware of their social behavior the patients were, the less activity was found in the temporal poles.

Table 1. Regions of Decreased Metabolism in 16 Patients with FTD Compared with 16 Age-matched Controls

Region	*Cluster Size*	*x*	*y*	*z*	*Z Score*
Left rectus gyrus	407	−4	30	−26	4.02*
Left subgenual area	407	−2	12	−14	3.63*
Left middle frontal gyrus	167	−40	50	20	4.04
Right inferior frontal gyrus	170	48	24	−18	3.66
Right superior frontal gyrus	10	14	34	58	3.45
Left temporal pole (superior)	11	−54	10	−6	3.41
Left temporal pole (middle)	32	−64	−6	−18	3.71

x, y, z = MNI coordinates. SPM threshold, $p < .0005$ uncorrected.

*$p < .05$ corrected, at cluster level.

DISCUSSION

This study provided quantitative measures of the characteristic social disability in FTD and identified a relationship between the metabolism of the left temporal pole and anosognosia for social disability.

Figure 3. Brain regions showing significantly lower FDG uptake at rest in patients with FTD than in control subjects ($p < .0005$, uncorrected).

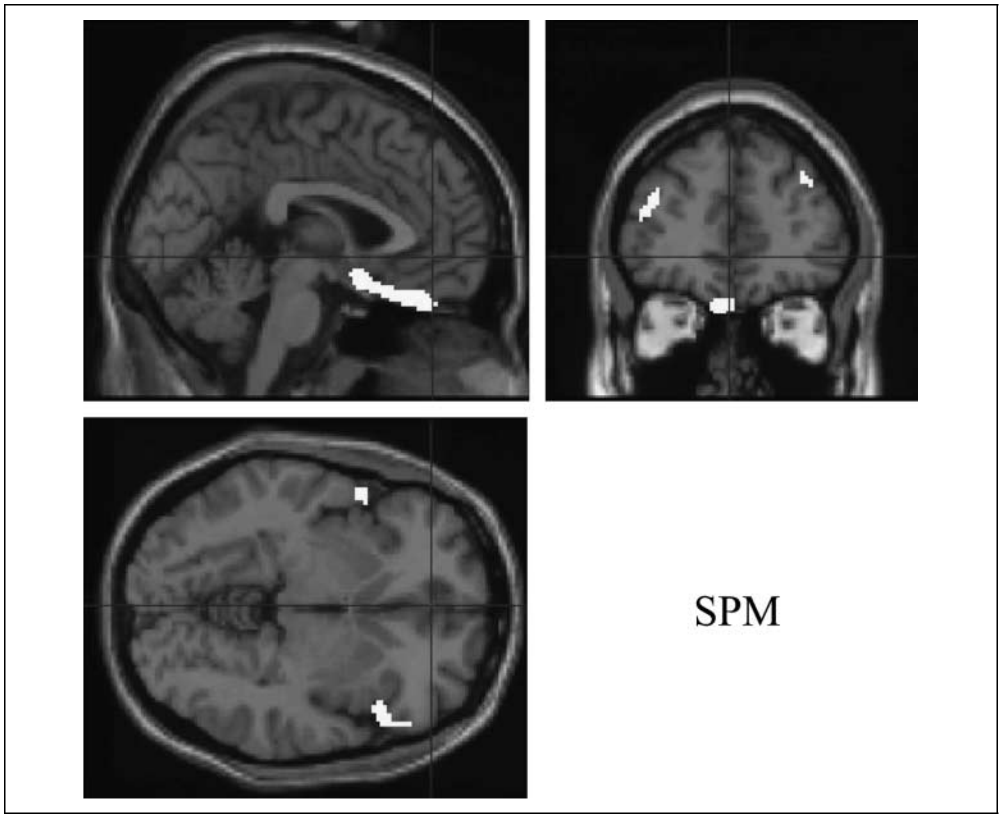
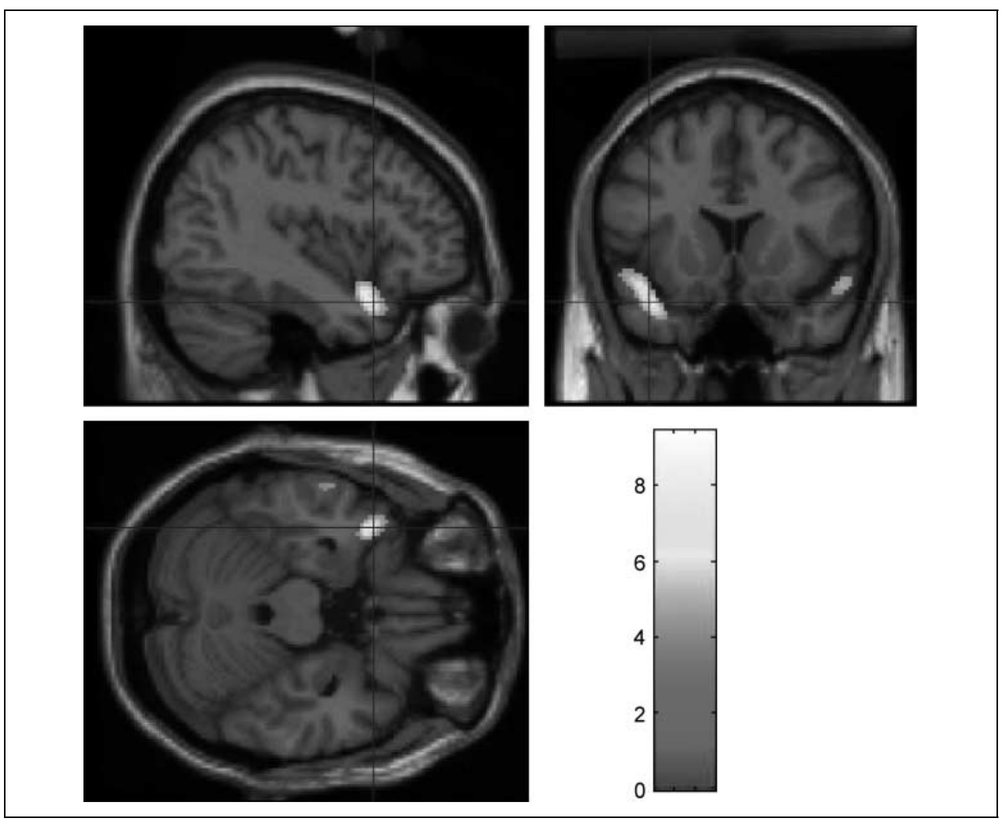


Figure 4. Sagittal, axial, and coronal sections of the brain at the MNI coordinates $x = -40$, $y = 12$, $z = -20$, showing the brain region in the left temporal pole demonstrating a significant correlation between cerebral metabolism and the score for anosognosia for social disability (S1–R3). $p_{(\text{corrected})} < .05$, Z score = 4.97, cluster extent = 315 voxels.



Reliability of Patients with FTD

Our opinion is that patients' answers are an open window on the psychopathological process taking place in early-stage fvFTD. Knowing that the reliability of patients with FTD has been questioned in the literature, one might be concerned by our use of patients' reports. However, several results in our study show that patients' answers are consistent and can therefore be used in a scientific study, even though they depart from reality.

The personality assessment questionnaire demonstrated that patients with FTD were as good as controls in assessing their relatives' personality (see S2–R1 in Figure 2). This result suggests that executive dysfunction did not prevent patients with FTD from evaluating personality. This was confirmed by the absence of any correlation between discrepancy scores and performance on executive tests.

As for the behavior prediction questionnaire, one could argue that patients with FTD had difficulty understanding complex sentences (Cooke et al., 2003; Grossman et al., 1998). We favor the hypothesis that their judgment is impaired over the hypothesis that they had trouble understanding the questions for two reasons. First, our patients did not have many difficulties handling complex sentences in the Concept subscale of the Dementia Rating Scale. Second, their personal impressions of changes over the past 10 years (S1bef–S1) showed that the patients were not providing random answers, but were as consistent during the session as were the control subjects. Hence, patients' self-evaluation turned out to be inaccurate, rather than inconsistent.

Personality and Behavioral Changes

The personality and behavioral changes observed during the last 10 years in subjects by their relatives (R2–R2bef and R3–R3bef) were significantly higher in the FTD group than in the control group. These results confirm, and also measure, the personality and behavioral alterations reported by the patients' relatives during their interviews with neurologists (Rankin et al., 2003; Neary et al., 1998). The congruence between the patient's previous personality/behavior and the relative's current personality/behavior was close to the control values (R1–R3bef and R1–R2bef). However, the congruence between both parties' current personality/behavior was significantly lower in the patient group (R1–R3 and R1–R2). These scores indicate that patients' personality and social reactions tend to move away from those of their relatives as the dementia progresses.

Third-person Perspective Taking in a Socioemotional Context

The results on the behavior prediction questionnaire confirmed our hypothesis that patients with fvFTD have impaired perspective-taking ability and corroborated previous studies that showed impaired mind representation in this disease (Gregory et al., 2002; Lough et al., 2001). Indeed, patients made more mistakes than did control subjects in predicting their relatives' reactions in a socioemotional situation (S3–R1), confirming the social cognition and perspective-taking deficit reported by relatives of patients with FTD (Rankin, Kramer, & Miller, 2005; Miller et al., 2003). This result with the fvFTD is congruent with a previous study showing activation of the medial prefrontal cortex and temporal pole in healthy subjects predicting their mothers' behavior in the same socioemotional situations (Ruby & Decety, 2004).

Interestingly, the accuracy of relatives' personality assessment (S2–R1) did not reveal any difference between the patient and control groups. However, patients with FTD had a deficit in semantic memory, inasmuch as they had not updated their knowledge of personality traits since their dementia had started. Indeed, according to our results, patients relied on old memories of personality traits both for self-assessment (S1–R2bef did not differ between the control and patient groups) and for their relatives' personality assessment (S2–R1 did not differ between groups). Lack of updating of knowledge of personality traits would not influence judgment of a relative's personality, because the relatives had not changed much in the past 10 years (as indicated by S1bef–S1 in the control group). On the other hand, patients made mistakes when predicting their relatives' behavior in socioemotional contexts. This complex perspective-taking process requires sensory and motor imagery, recall of autobiographical (episodic and semantic) memories, coordinate transformation, inductive reasoning, and the distinction between self and other representation. Several of those processes are impaired in FTD, which would explain the patients' false and odd predictions.

No significant correlation was found between the discrepancy score reflecting impaired perspective taking in social situations (S3–R1) and resting brain FDG uptake in patients with FTD. This absence of correlation may be related to the fact that the neural network subserving perspective taking is distributed (Ruby & Decety, 2004) and patients have different levels of metabolic impairment in each region of the network. Reduced metabolism in any one of these regions would impair perspective-taking ability, but no region is individually related to the discrepancy score measured in patients with fvFTD.

Egocentric Bias in Third-person Perspective Taking

The egocentricity (S1–S3) score was around 45% in patients with FTD, which was not significantly different from the score for control subjects. This result suggests that patients were able to distinguish between themselves and another person when they predicted behavior in concrete social situations. Contrary to our prediction and the results of Snowden et al. (2003), patients with FTD did not demonstrate increased egocentric bias in third-person perspective in an emotional context. Snowden et al. reported an egocentric bias in patients with FTD when they had to identify the picture that a cartoon character preferred based on direction of gaze. The wrong answers of patients with FTD often reflected their own preference. The discrepancy between these results and our own may originate in the different paradigms used. Patients with FTD may be especially strongly influenced by visual stimuli and may have great difficulty preventing themselves from looking at their own preferred image (lack of control/inhibition of the external influence especially in the visual modality). Hence, an egocentric bias might be more salient in the visual modality than in a conceptual modality.

Anosognosia for Personality and Behavioral Changes

Anosognosia for current personality/behavior changes was significantly higher for the FTD group than for the control group. The disagreement between the relatives' answers about the patients' current personality/behavior and the patients' assessment of their current personality/behavior (S1–R2 and S1–R3) is considered as a measure of their "loss of insight," a core diagnostic feature of FTD (Rankin et al., 2005; Neary et al., 1998). Moreover, self-assessment of personality/behavioral changes over the past 10 years (S1bef–S1) did not differ between the FTD and control groups for both questionnaires. These scores reveal that the patients were not aware of the pathological behavioral changes that had occurred over the past 10 years.

Interestingly, no correlation was found between the two scores of anosognosia (S1–R3 and S1–R2), and our results suggest that different cognitive components are involved in both types of anosognosia (for own behavioral change or for personality change), as already discussed in the case of third-person perspective taking. Patients' own behavioral predictions are very different (much more so than those of controls) from "how their relatives see them now" and also from "how their relatives remember them 10 years ago" (see S1–R3 and S1–R3bef in Figure 2). This result suggests that patients' false judgment of their own current reactions in socio-emotional situations did not originate only in reliance on old (non-updated) memories of their reactions before dementia onset. On the contrary, the results on the personality questionnaire demonstrated that patients' own personality assessment is very different (much more than controls) from how their relatives see them now but not (no more than controls) from how their relatives remember them 10 years ago (S1–R2 and S1–R2bef), suggesting that patients succeeded in accessing old (non-updated) memories of their personality traits. This result interestingly resemble that reported in one patient with Alzheimer's disease who demonstrated correct but non-updated self-personality representation (Klein et al., 2003). Our study was not designed to explore why personality traits were not updated in fvFTD. However, it is noteworthy that posterior orbitofrontal dysfunction has been found to be related to impaired updating of self-knowledge in Alzheimer's disease (Salmon et al., 2006).

Correlation analysis between discrepancy scores and metabolic activity was also in favor of dissociation because regional metabolic activity was found to be significantly correlated only with anosognosia for behavioral changes in social situations (S1–R3) but not with anosognosia for personality changes (S1–R2). The more anosognosic a patient is of behavioral changes, the less active the temporal pole is, especially in the left hemisphere (Figure 4). A key to understanding the involvement of the left temporal cortex in anosognosia for social behavior may be its recruitment for memory and emotional processing. In healthy subjects, both the retrieval of personally relevant and time-specific memories and the perception of emotional stimuli is associated with enhanced activity in the left temporal pole (Graham, Lee, Brett, & Patterson, 2003; Pelletier et al., 2003; Royet et al., 2000; Maguire, Frith, & Morris, 1999). Along the same lines, the temporal pole has been shown to be more activated for emotional than for neutral memory recall (Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003; Dolan, Lane, Chua, & Fletcher, 2000). Hence, the significant correlation between the score of anosognosia for behavioral change in social situations and the metabolic activity in the temporal pole of patients with fvFTD suggests that anosognosia for social disability in fvFTD originates in a retrieval and utilization deficit affecting autobiographical information involving the self in socioemotional interactions. This impaired processing of personal and emotional events in memory would cause a self-representation that does not match the current behavior.

Moreover, a deficit in processing emotional memories may not be sufficient to explain why patients with fvFTD are not aware of a self-representation that does not match their actual behavior. In pathologies such as Alzheimer's disease or schizophrenia, patients may have inaccurate memories and an unrealistic self-representation but are able to notice this discrepancy using feedback from the outside world such as other people's comments and reactions (Salmon et al., 2005; Gambini, Barbieri, & Scarone, 2004).

From the point of view of social psychology, social emotions such as the ones examined in this study (i.e., guilt, shame, embarrassment, pride) are called "self-conscious emotions." Such emotions are founded in social relationships and arise from concerns about others' opinions of oneself or one's behavior. This means that, in healthy subjects, evaluating one's own self-conscious emotions already involves taking another person's perspective of oneself (Takahashi et al., 2004; Gilovich, Medvec, & Savitsky, 2000; Fenigstein & Abrams, 1993). We suggest that impaired third-person perspective (S3–R1) in patients with fvFTD most probably also contributes to their impaired self-representation in social situations, preventing them from adjusting or correcting their social self-representation based on external feedback. In that sense, perspective-taking ability appears to be a decisive component in building a self-representation in accordance with one's actual behavior. Hence, self- and other representation capacities appear to be intrinsically linked, and just as the first-person perspective influences one's perspective of other people (Gallese, Keysers, & Rizzolatti, 2004; Grezes & Decety, 2001; Gilovich et al., 2000; Meltzoff, 1999; Davis, Conklin, Smith, & Luce, 1996), the third-person perspective—allowing one to represent others' perspective on the self—is proposed to be a component of self-representation.

Our hypothesis concerning patients with fvFTD fits well with previous results obtained both in neurology and in psychiatry. Some patients who were unaware of their deficits, whether paralysis after a right-hemisphere stroke or delusions in schizophrenia, when interviewed from a first-person perspective, have been reported to gain some insight into the deficit when interviewed from a third-person perspective (Gambini et al., 2004; Marcel, Tegner, & Nimmo-Smith, 2004). Even though the spontaneous link between first- and third-person perspective appears to be disrupted in those patients, the importance of the third-person perspective in self-representation appears clearly, because these patients may take new information about the self into account when they apply another person's perspective.

Conclusions

In this study, we compared answers by patients with fvFTD and their relatives on the topic of personality assessment and behavior prediction in social and emotional situations. We measured drastic behavioral changes, impaired perspective taking, and anosognosia for personality and behavioral alterations. The level of metabolic activity in the left temporal pole was shown to correlate with the severity of anosognosia for behavioral changes in social situations. These results shed light on social mind representation and suggest that anosognosia for social disabilities is not related to a general executive dysfunction but rather to an impaired processing of social/emotional autobiographical information. Such impaired processing would lead to an inability to remember the self as it behaves in social interactions. Moreover, a perspective-taking disability would prevent patients with FTD from correcting their inaccurate self-representations on the basis of other people's perceptions of their behavior.

Acknowledgments

This work was supported by the National Fund for Scientific Research (FNRS), by the University of Liège, by the InterUniversity Attraction Pole P 5/04, by the EC FP6 project DiMI, LSHB-CT-2005-512146, and by the European Community, which granted P. Ruby a Marie Curie Individual fellowship. F. Collette and A. D'Argembeau are FNRS researchers.

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