Primary empathy deficits in frontotemporal dementia

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Words for abstract: 240; words for article body: 3.558
Number of figures: 3; number of tables: 2
Supplementary material: S1: Methods; S2: Results; Video 1: Examples of the empathy for pain task stimuli

Key words: Behavioral variant of frontotemporal dementia, empathy, empathic concern, social cognition, executive functions, moral judgment.

Abstract

Background: Loss of empathy is an early central symptom and diagnostic criterion of the behavioral variant frontotemporal dementia (bvFTD). Although changes in empathy are evident and strongly affect the social functioning of bvFTD patients, few studies have directly investigated this issue by means of experimental paradigms. The current study assessed multiple components of empathy (affective, cognitive and moral) in bvFTD patients. We also explored whether the loss of empathy constitutes a primary deficit of bvFTD or whether it is explained by impairments in executive functions (EF) or other social cognition domains.

Methods: Thirty-seven bvFTD patients with early/mild stages of the disease and 30 healthy control participants were assessed with a task that involves the perception of intentional and accidental harm. Participants were also evaluated on emotion recognition, theory of mind (ToM), social norms knowledge and several EF domains.

Results: BvFTD patients presented deficits in affective, cognitive and moral components of empathy. However, empathic concern was the only aspect primarily affected in bvFTD that was neither related nor explained by deficits in EF or other social cognition domains. Deficits in the cognitive and moral aspects of empathy seem to depend on EF, emotion recognition and ToM.

Conclusions: Our findings highlight the importance of using tasks depicting real-life social scenarios because of their greater sensitivity in the assessment of bvFTD. Moreover, our results contribute to the understanding of primary and intrinsic empathy deficits of bvFTD and have important theoretical and clinical implications.

1. Introduction

Loss of empathy is an early symptom of behavioral variant of frontotemporal dementia (bvFTD) and constitutes one of its diagnostic criteria (1, 2). Patients with bvFTD display a diminished response to other's feelings and a diminished social interest or personal warmth (3, 4). From a clinical perspective, empathy changes influence the interpersonal judgment, emotions, behavior, and social functioning of bvFTD patients (1, 2, 5). In spite of its relevance, the study of empathy in bvFTD patients using experimental designs has been scarce, and no studies have explored whether relevant factors (6, 7) such as executive functions (EF) and other social cognition domains (OSCD) impact the empathic abilities of these patients.

The current study assessed multiple empathy aspects in bvFTD patients using an experimental paradigm of empathy for pain that has been previously validated with behavioral measures, eye-tracking and fMRI (8). Moreover, we explored whether empathy deficits constitute a primary symptom of bvFTD or whether they are secondary to EF or OSCD impairments.

Empathy is essential for human social interaction, comprising the capacity to share and understand the subjective experience of others in reference to oneself (9). This complex construct involves (1) affective components: sharing and responding to the emotional experience of others (10); (2) cognitive components: understanding the intentions and perspectives of others; and (3) moral components: judging the actions of a perpetrator or the punishment deserved (8, 9).

In spite of the complexity of empathy, traditional approaches to measure it have relied on self-report questionnaires. These questionnaires do not allow appropriate measurements (they consider empathy as a trait) and do not fully represent empathic abilities because of their limited ecological validity (11). Most studies of empathy with bvFTD patients (3, 5, 12, 13) have employed self-report questionnaires, evidencing impairments in affective and cognitive components.

We implemented a novel paradigm with naturalistic stimuli that measures empathy for other's physical pain. This type of paradigm has been widely used due to the robustness of pain in inducing empathic responses (14) and the well characterized neural circuit of empathy (15). The empathy for pain task (EPT) employed here (16, 17) evaluates empathy in the context of intentional/accidental harms and consists of three different scenarios: (1) intentional or (2) accidental harms in which one person is in a painful situation intentionally or accidentally caused by another, and (3) neutral or control situations. The EPT evaluates the following components: (A) comprehension of the accidental or deliberate nature of the action and the intention of the perpetrator to hurt (cognitive components), (B) the empathic concern and the degree of discomfort for the victim (affective components), (C) the correctness of the action and punishment for the perpetrator (moral components).

Executive functions and OSCD seem to affect Individual differences in empathy(18, 19) as well as in emotion processing (18), ToM (19) and moral cognition (8) have been linked to empathy. Indeed, neuroimaging studies (18) show overlapped brain regions among these processes. It is well known that both EF (6, 20, 21) and social cognition (22, 23) are impaired in bvFTD, but there are no studies exploring whether and how these factors affect the empathic abilities these patients. This study assessed multiple empathy components in bvFTD patients by using an experimental paradigm involving ecological validity. We also employed several EF and OSCD (emotion recognition, ToM, and social norms knowledge) sensitive measures for bvFTD assessment. Finally, we explored whether empathy deficits constitute a primary symptom of bvFTD or if they are an EF or OSCD impairments consequence.

2. Methods and Materials

2.1. Participants

Thirty-seven patients fulfilled the Lund and Manchester criteria (24) and the revised criteria for probable bvFTD (2) (see details regarding phenocopies or differential diagnoses in S1). Patients presented with prominent changes in personality and social behavior as verified by caregivers. Diagnosis was made by a group of experts in bvFTD. Patients underwent a standard examination battery including neurological, neuropsychiatric and neuropsychological assessments and a routine MRI. All patients were in early/mild stages of the disease and did not meet the criteria for specific psychiatric disorders. Patients presenting primarily with language deficits were excluded.

The performance of bvFTD patients was compared with that of 30 healthy matched control subjects without a history of psychiatric or neurological diseases (Table 1). All participants provided written informed consent in agreement with the Helsinki declaration. The Ethics Committee of the Institute of Cognitive Neurology approved this study.

2.2. Instruments

General cognitive state (Mini-Mental State Examination, MMSE) and premorbid IQ (Word Accentuation Test) were assessed. See supplementary material S1.

2.2.1. Empathy assessment

The EPT evaluates empathy in the context of intentional and accidental harms (8, 16, 17) and consists of 25 animated scenarios (11 intentional, 11 accidental, 3 neutral) involving two individuals. Each scenario consists of 3 digital color pictures presented in a successive manner to imply motion. The durations of the first, second, and third pictures in each animation were 500, 200, and 1000 ms, respectively (Figure 1, Video 1). The three following types of situations were depicted: intentional harm in which one person is in a painful situation intentionally caused by another, (e.g., purposely stepping on someone's toe); accidental harm where one person is in a painful situation accidentally caused by another; and control or neutral situations (e.g., one person receiving a flower given by another).

Importantly, the faces and emotional reactions of the protagonists are not visible to the participants. We measured the reaction times (RTs) to situation comprehension ("press the button as soon as you understand the situation"). Furthermore, participants were asked to respond 6 questions: (1) cognitive aspects of empathy: intentionality (the accidental or deliberate nature of the action) and intention of the perpetrator to hurt the victim (how bad was the purpose?); (2) affective aspects: emphatic concern (how sad do you feel for the victim?) and degree of discomfort (for the victim); and

(3) moral evaluation aspects: correctness of the action and punishment (how much penalty does this action deserve?). Each question was answered using a computer-based visual analogue scale (Figure 1, Video 1). Ratings and RTs for each question were measured.

Before testing, all participants performed a training session consisting in a shorter version of the task with similar situations to ensure the correct understanding of the instructions.

2.2.2. OSCD

The OSCD assessment included: A) The Awareness of Social Inference Test (TASIT), which is used to assess emotion recognition and can detect subtle deficits in bvFTD (25); B) the Reading the Mind in the Eyes Test (RMET), a ToM task sensitive for bvFTD impairments (21); and C) the Social Norms Questionnaire (SNQ), an instrument employed in the assessment of bvFTD patients (6). Before each test, participants performed training trials to make sure that the instructions were understood. See supplementary material S1.

2.2.3. EF

The EF battery included the INECO frontal screening (IFS) (26), and measures of verbal fluency, inhibitory control, speed processing, working memory and cognitive flexibility. See S1.

2.3. Data Analysis

ANOVA and Tukey's HSD post hoc test (when appropriate) were used to analyze differences among groups. To control for general cognitive state on performance, we applied ANCOVA tests adjusted for the MMSE scores (reporting only effects that were still significant after covarying). To determine whether empathy deficits were related to EF or OSCD, the empathy results were re-analyzed using the total scores of all measures of OSCD and EF independently as covariates (see (21) for a similar approach). These analyses were conducted separately. Finally, we conducted multiple regression analyses to explore whether empathy performance was partially explained by specific impairments in EF or OSCD. The empathy measures that were still significantly different between groups after any of the covariance analyses were separately considered as dependent variables. We estimated two different models in which the empathy measures that were still significantly different between groups after any of the covariance analyses were considered as dependent variables. The first model included a global score of intentionality (the mean of the three conditions) as dependent variable; the second one considered as dependent variable a score of empathic concern defined by the subtraction of neutral situations from the intentional ones. The group, the gender, a global score of OSCD (mean accuracy on TASIT and RMET) and the IFS total score were included as predictors.

3. Results

3.1. Demographic data and general cognitive state

Groups were matched by age ($F(1,65)=0.10$, $p=0.74$), gender ($X^2(1)=0.59$, $p=0.44$), education ($F(1,65)=0.97$, $p=0.32$) and premorbid IQ ($F(1,65)=1.54$, $p=0.21$). As expected, bvFTD patients showed lower MMSE performance than controls ($F(1,65)=11.55$, $p<0.01$) (Table 1).

3.2. Empathy

Results are summarized in Figure 2.

Cognitive components. Significant differences between groups ($F(2,120)=3.15$, $p<0.05$) were observed in intentionality judgments. Post-hoc analysis (Tukey's HSD, MS=464.81, df =179.92) revealed that bvFTD patients (hereafter referred to as patients) had significantly lower comprehension of the intentionality of accidental ($p<0.01$) situations compared to controls. Furthermore, differences between groups were observed in ratings of intention to hurt ($F(2,120)=16.44$, $p< 0.01$). Post-hoc analysis (Tukey HSD, MS=10.29, df=23.72) showed that patients had higher ratings than controls for neutral ($p<0.05$) and accidental ($p<0.01$) situations.

Affective components. The empathic concern ratings were significantly different between groups ($F(2,120)=10.02$, $p<0.01$). Post-hoc analysis (Tukey HSD, MS=10.69, df=155.04) revealed that patients rated intentional pain situations lower

($p<0.05$) than controls. Furthermore, controls showed higher empathic concern for intentional than accidental pain situations ($p<0.01$). This difference was not observed in patients ($p=0.78$).

Moral components. Significant differences were found in correctness ratings ($F(2,120)=513$, $p<0.01$). Post-hoc analysis (Tukey HSD, MS=9.62, df=170.63) showed that patients rated neutral situations as more incorrect than controls ($p<0.01$). Between groups, differences ($F(2,120)=6.24$, $p<0.01$) were also found in punishment. Post-hoc analysis (Tukey's HSD, MS =11.21, df=127.24) showed that patients rated neutral ($p<0.01$) situations higher than controls.

No RTs differences were observed between groups.

3.3. Social cognition and EF

The OSCD and EF results are shown in Table 1 (see details in supplementary material S2). Regarding social cognition, patients showed lower performance on TASIT (as well as scores of sadness, fear and disgust recognition) and RMET scores than controls. No group differences were observed in SNQ scores. Regarding EF, patients showed a lower performance than controls on the IFS total score, cognitive flexibility, the Hayling test and the verbal phonological fluency task.

3.4. Re-analysis of empathy data with social cognition measures as covariates

Group differences in the intentionality comprehension (accidental pain situations) remained significant after adjusting for OSCD ($F(1,65) = 5.72$, $p < 0 .05$). Similarly, group differences in empathic concern for intentional pain situation were preserved (F(1,65) = 6.98, p < 0 .05). Nonetheless, differences in intention to hurt ratings for neutral (F(1,65) = 0.95, p = 0.33) and accidental situations (F(1,65) = 4.00, p = 0.06) were not preserved after co-varying. Differences between groups in correctness (F(1,65) = 2.03, p = 0.15) and punishment (F(1,65) = 2.63, p = 0.11) ratings for neutral situations also disappeared. See figure 2A and C.

3.5. Re-analysis of empathy data with EF as covariates

Group differences in the intentionality comprehension did not remain significant after adjusting for EF (F(1,65) = 2.24, p = 0 .14). A significant effect of the Hayling test performance on accidental situations comprehension was also observed (F(1,65) = 6.47, p < 0 .05).

Significant group differences in empathic concern ratings for intentional pain situation were preserved (F(1,65) = 16.53, p < 0 .01) after covariate analysis (Figure 2C). However, differences in intention to hurt ratings for neutral (F(1,65) = 0.01, p = 0.89) and accidental situations (F(1,65) = 1.07, p = 0.30) were not preserved after co-varying, as well as correctness (F(1,65) = 0.12, p = 0.72) and punishment (F(1,65) = 0.047, p = 0.82) ratings for neutral situations.

3.6. Is the empathy performance partially explained by EF, OSCD or general cognitive state?

Figure 3 shows associations in multiple regression analyses indexing the role of EF and OSCD. A first model including the intentionality score as dependent variable

($F(1,65) = 8.59$, $p < 0.01$) showed that EF (beta = 0.28) and group (beta = -0.29) predicted the intentionality comprehension, explaining 38% of the variance. We carried out a second model with empathic concern as dependent variable (subtraction of neutral situations from the intentional ones). This model ($F(1, 65) = 5.02$, $p < 0.01$) evidenced that group (but not EF or OSCD) was the only predictor (beta = -4.14) associated with empathic concern ratings, explaining 26% of the variance.

To confirm this last result, we estimated three different multiple regression models considering empathic concern as dependent variable and including sequentially all the EF and OSCD covariables. The first model including all EF variables showed that none of them were significantly associated ($F(1, 65) = 0.54$, $p = 0.73$). The second model including all OSCD variables ($F(1, 65)=0.14$, $p=0.93$) evidenced no significant associations. The third model included all EF and OSCD variables confirmed that none of these measures were significantly associated with empathic concern ($F(1, 65)=0.23$, $p=0.96$) (see Table 2).

In brief, EF predicted the intentionality comprehension but not the empathic concern. Social cognition was not associated with any of the dependent variables. Empathic concern was not explained by any predictor.

To explore whether empathic concern depends on the general cognitive state or disease severity, we also compared the performance of patients with high (54%) and low (46%) MMSE scores (cut-off=27). No group differences in empathic concern ($t(35)=0.80$, $p=0.42$) were found, suggesting an early and primary involvement.

4. Discussion

Although empathy deficits are considered a central feature and diagnostic criterion of bvFTD, no studies had directly explored the contribution of different empathy aspects and whether and how factors such as EF and social cognition affect the empathic abilities in these patients. Our results replicate previous findings of EF (21, 26) and social cognition (6, 22) impairments in bvFTD (except for the lack of differences in SNQ scores (6), that would be explained by population's cultural differences). Moreover, we provide evidence of a primary deficit in empathic concern that is not explained by deficits in EF or OSCD. The identification and further assessment of the primary empathy deficits of bvFTD patients may be useful in the establishment of behavioral patterns and potentially in predicting the disease progression based on empathic concern levels.

4.1. Differential impairments of empathy components

Impaired cognitive components (distinguishing accidental from neutral and intentional situations) were observed in patients. This is expected because empathy is a contextual phenomenon affected by stimulus ambiguity (27). Contextual cues help to bias the intrinsic meaning of ambiguous targets (28), particularly regarding others in pain (27). Accidental pain situations are less clear and explicit and increase the level of ambiguity and the demands in the attribution of the action's intentionality. Patients with bvFTD have deficits in inferring the intentionality of others' actions (7, 21, 29), and in understanding ambiguous emotional scenes (30). Furthermore, results are consistent with the current view that these patients have deficits in processing contextual social cues (23, 24).

Patients rated the intention to hurt for neutral/accidental situations higher than controls. In contrast, empathic ratings of healthy participants (8, 15) are greater for intentional than for accidental pain situations. Intentionality detection is a decisive step in determining whether an action was malicious (8). The inability to infer the intentions of others' actions may affect the intention to hurt ratings. Patients with bvFTD tend to overattribute bad intentions to the agent (7, 31), even if the action was unintentional.

Regarding affective components, bvFTD patients showed lower empathic concern ratings for intentional pain situations. Previous bvFTD studies (3, 5, 12) have reported diminished levels of empathic concern as rated by relatives or caregivers. Thus, this characteristic appears to be a core component of bvFTD empathy impairments (see below).

On moral components, patients rated neutral situations more morally wrong than controls. However, neutral situations did not represent a wrong action. Again, these findings suggest deficits in inferring the intentionality of the action and in attributing bad intention even when this was not the purpose. Moral reasoning relies on both affective and cognitive processes to integrate intentions and action consequences (8). In agreement with previous reports (4, 5, 32), our results suggest that moral reasoning is impaired in bvFTD.

Overall, the empathy profile of patients was characterized by impairments in cognitive, affective and moral components. Deficits in the ability to infer the intentionality of another's actions seem to affect cognitive and moral components. Empathic concern was the only component primarily affected in bvFTD.

4.2. Are empathy deficits explained by EF or OSCD?

Impairments in the cognitive components of bvFTD patients remained significant after adjusting for social cognition but disappeared after co-varying for EF. Working memory, selective attention and inhibitory control (13, 18, 19) are particularly associated with cognitive empathy. Specifically, inferring the intentionality of an action requires the inhibition of one’s own perspective and the simultaneous appraisal of contextual cues (13). During EPT, accidental pain situations are less clear and explicit. Therefore, it is possible that the accurate recognition of these situations requires a higher EF demand.

Similarly, the significance of intention to hurt and correctness/punishment ratings also disappeared after co-varying for EF. These three empathy aspects are strongly dependent on the observer’s interpretation of intention, and the EF profile seems to explain these deficits. In bvFTD (5, 12), a relationship between cognitive components (rated by caregivers) and EF has been evidenced. The same group differences also disappeared after co-varying for social cognition, consistent with the fact that empathy depends on emotion recognition (18, 33) and ToM (19, 34). Moreover, the deficits in moral components in bvFTD patients may be partially explained by an empathic loss in emotionally identifying with others (32). Thus, emotion recognition and ToM deficits account for the abnormalities in cognitive and moral components of empathy observed in patients with bvFTD.

Differences in empathic concern for intentional situations remained significant after co-varying for EF and OSCD. These results suggest that bvFTD patients have a core deficit in other-oriented emotional reactions to the misfortune of others. We performed multiple regressions to further explore which empathy aspects were primary affected. We choose a global score of the OSCD from TASIT and RMET because in this and previous studies (21, 25) detected bvFTD impairments. The IFS was also selected as a predictor because this tool includes several EF subtests and detects bvFTD executive dysfunction (26). Multiple regression results showed that empathic concern was not predicted by EF or OSCD.

4.3. Emphatic concern as the primary affectation of bvFTD

Taken together, our results suggest that empathic concern is the only component primarily affected in bvFTD that is neither related nor explained by EF/OSCD deficits or the general cognitive status. In contrast, deficits in cognitive and moral aspects of empathy seem to depend on other processes such as EF, emotion recognition or ToM.

The degree of discomfort (an affective component) was preserved in patients. Unlike empathic concern, the discomfort degree involves self-oriented feelings of personal unease when exposed to the suffering of others (35). Moreover, discomfort may produce an egoistic motivation to reduce one’s own personal distress, whereas empathic concern may instigate an altruistic motivation to help the other. Thus, the other-oriented emotional response that produces a motivational state to increase the other's welfare was intrinsically affected in bvFTD, constituting the core of empathy impairments observed in these patients.

Theoretical approaches (9) and empirical evidence (3) agree that empathy relies on dissociable affective and cognitive components. Emotional components of empathy are foundational, while cognitive components are more complex and may depend upon other abilities (3). Thus, diminished other-oriented emotional responses may be sufficient to produce the daily empathy impairments observed in bvFTD patients.

Neuroimaging studies of empathy (3, 36) highlight a network that includes the inferior and medial frontal cortex, amygdala, right somatosensory cortex, right temporal pole and insula; all brain areas usually affected in bvFTD (37-39). The brain atrophy pattern in bvFTD is consistent with the primary deficit in empathic concern observed in this study. Our findings open new pathways to investigate whether impairments in empathic concern could predict the atrophy pattern, behavioral changes, and the clinical profile of bvFTD. Although this is the first study in evidencing the empathic concern deficits usually reported by bvFTD relatives by means of a experimental method, our patients were investigated only with routine MRI recordings. Further volumetric and fMRI studies may provide additional insights about the relationship among the location of atrophy and the associated pattern of empathy impairments.

From a clinical perspective, given that adequate empathic functioning is an important element of higher social functioning (13), such an impairment should be considered in the assessment and treatment of bvFTD. Furthermore, one of the strengths of the current study is its reliance on an ecological design that is more appropriate than self-report questionnaires. It is well-known that even frontal patients are impaired in their everyday lives. It is difficult to detect impairments with traditional tests because standard and decontextualized neuropsychological assessments introduce sufficient external structure to suppress some behavioral tendencies (40). Remarkably, the task employed here detected experimentally (5, 12). The convergence between observations in experimental, clinical and everyday life highlight the importance of considering empathic concern impairments as a core symptom of bvFTD. These results emphasize the value of using tasks involving real-life social scenarios (21, 23) as evidenced by their greater sensitivity in the assessment of neuropsychiatric populations. A more subtle understanding of these complex cognitive deficits in bvFTD will improve assessment in the clinical setting and may allow for the development of rational cognitive stimulation strategies.

Acknowledgements

This research was partially supported by grants CONICYT/FONDECYT Regular (1130920), PICT 2012-0412 and PICT 2012-1309 (A Ibanez), CONICET and INECO Foundation.

Financial Disclosures

Dr. Ibanez reports having received research funding from CONICYT/FONDECYT Regular (1130920), PICT 2012-0412 and PICT 2012-1309. The other authors report no disclosures relevant for this manuscript. The authors declare no competing financial interests.

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Figure Legends

Figure 1. (A) Examples of the visual stimuli used for each category. The durations of the first, second, and third picture were 1000 ms, 200 ms, and 1000 ms, respectively. **(B) Examples of the questions designed to assess different empathy aspects**. Each question was answered using a computer-based visual analogue scale.

Figure 2. Performance in the empathy for pain task and significant differences between groups. Differences that were statistically significant are indicated by * (before co-varying), ** (after co-varying by social cognition measures), and *** (after co-varying by EF). (A) Intentionality judgments. NS=neutral situations, IPS=intentional pain situations, APS=accidental pain situations. (B) Empathy ratings for neutral situations. (C) Empathy ratings for intentional pain situations. The highlighted region shows empathic concern as the only difference that remained significant after covariate adjustment for social cognition ($F(1,65) = 6.98$, $p < 0 .05$) or executive functions ($F(1,65) = 16.53$, $p < 0 .01$). (D) Empathy ratings for accidental pain situations. IH=intention to hurt, EC=empathic concern, D=discomfort, C=correctness, P=punishment.

Figure 3. Multiple regression analyses. (A) Regression analysis using intentionality comprehension as the dependent variable. Executive functions significantly predicted the intentionality comprehension. (B) Regression analysis using empathic concern as the dependent variable. No significant associations were observed between empathic concern and social cognition or executive functions.