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Behavioural neurology

Orbitofrontal and limbic signatures of empathic concern and intentional harm in the behavioral variant frontotemporal dementia

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ABSTRACT

Perceiving and evaluating intentional harms in an interpersonal context engages both cognitive and emotional domains. This process involves inference of intentions, moral judgment, and, crucially, empathy towards others' suffering. This latter skill is notably impaired in behavioral variant frontotemporal dementia (bvFTD). However, the relationship between regional brain atrophy in bvFTD and deficits in the above-mentioned abilities is not well understood. The present study investigated how gray matter (GM) atrophy in bvFTD patients correlates with the perception and evaluation of harmful actions (attribution of intentionality, evaluation of harmful behavior, empathic concern, and moral judgment). First, we compared the behavioral performance of 26 bvFTD patients and 23 healthy controls on an experimental task (ET) indexing intentionality, empathy, and moral cognition during evaluation of harmful actions. Second, we compared GM volume in patients and controls using voxel-based morphometry (VBM). Third, we examined brain regions where atrophy might be associated with specific impairments in the patient group.

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Moral judgment
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Finally, we explored whether the patients' deficits in intentionality comprehension and empathic concern could be partially explained by regional GM atrophy or impairments in other relevant factors, such as executive functions (EFs). In bvFTD patients, atrophy of limbic structures (amygdala and anterior paracingulate cortex – APC) was related to impairments in intentionality comprehension, while atrophy of the orbitofrontal cortex (OFC) was associated with empathic concern deficits. Intentionality comprehension impairments were predicted by EFs and orbitofrontal atrophy predicted deficits in empathic concern. Thus, although the perception and evaluation of harmful actions are variously compromised in bvFTD, deficits in empathic concern may be central to this syndrome as they are associated with one of the earliest atrophied region. More generally, our results shed light on social cognition deficits in bvFTD and may have important clinical implications.

1. Introduction

Suppose you are at a birthday party and a man suddenly appears holding a large knife. This person walks to the table where the cake is placed. How would you react? Would you feel threatened? Probably you would not startle because you would quickly understand that he does not intend to hurt anybody; he is simply going to cut the birthday cake. Now imagine that this man deliberately attacks someone with the knife. You would then automatically identify his behavior as harmful, feel empathic concern for the victim, and assess the action as morally wrong. The ability to detect intentional harms is early processed by frontotemporal networks (Hesse et al., 2015), and involves several skills, such as intentionality detection, empathy, and moral judgment (Decety & Cacioppo, 2012; Decety, Michalska, & Kinzler, 2012; Escobar et al., 2014). These abilities are essential for human survival and successful social interaction.

Our estimation of an action's harmfulness depends on whether we perceive it as intentional or accidental (Decety, Michalska, & Akitsuki, 2008; Decety et al., 2012). In addition, empathic concern is higher when a person inflicts pain on another one intentionally rather than accidentally (Decety et al., 2012). By the same token, the estimation of how severely punished an actor should be in the above situations depends on the assessment of his/her intentionality (Treadway et al., 2014). Thus, detection of the intentionality plays a crucial role in how harmful actions are perceived, and it also affects moral judgments and empathic responses (Decety et al., 2008).

Observing intentional harms elicits empathic reactions (Bernhardt & Singer, 2012; Decety et al., 2012) critical for successful social functioning (Rankin, Kramer, & Miller, 2005). Loss of empathy is a cardinal symptom of the behavioral variant of frontotemporal dementia (bvFTD), which constitutes a clue for early diagnosis (Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011). Patients with bvFTD lack concern for other's feelings (Rankin et al., 2006) and are described by relatives as selfish and self-centered (Hsieh, Irish, Daveson, Hodges, & Piguet, 2013). Empathy changes may thus be presumed to underlie this population's difficulties in interpersonal judgment, emotions, behavior, and social functioning (Lough et al., 2006; Piguet et al., 2011; Rascovsky et al., 2011).

At the neuroanatomical level, empathy processes engage a broad network including the insula, the anterior cingulate cortex (ACC), the supplementary motor area (SMA), the amygdala, the orbitofrontal cortex (OFC), and the temporoparietal junction (Bernhardt & Singer, 2012; Fan, Duncan, de Greck, & Northoff, 2011; Singer & Lamm, 2009). Notably, several studies on bvFTD have reported a reduction of gray matter (GM) in most of these areas (Rosen et al., 2002; Seeley et al., 2008). However, at present, the relationship between atrophy in such regions and the empathy deficits observed in bvFTD patients is not well understood.

Only three studies have investigated the neural basis of empathic impairments in bvFTD. Two of them (Eslinger, Moore, Anderson, & Grossman, 2011; Rankin et al., 2006) reported associations between caregivers' ratings on a self-report questionnaire and reduced GM volumes in ventromedial frontal regions, the right SMA, the right subcallosal gyrus, the bilateral temporal poles, the right fusiform gyrus, and the right amygdala. The third study (Cerami et al., 2014) compared two components of empathy (intention attribution and emotion attribution), and correlated them with reduced GM density within the mentalizing network. Specifically, emotion attribution performance in the patients correlated with GM reduction in the right amygdala, left insula, and posterior-superior temporal sulcus –extending into the temporoparietal junction. However, neither these nor any other studies have yet investigated how the atrophy pattern of bvFTD correlates with empathic responses (and their related evaluation of intentionality and moral judgment) elicited by the perception of harm to others.

Over the last decade, several studies in healthy and clinical populations have employed representations of harmful actions to others (e.g., infliction of pain) as proxies to investigate different aspects of empathy, intention attribution, and moral judgment. The evidence thus demonstrates that the perception of harmful actions robustly induces empathic and moral responses (Decety & Cacioppo, 2012; Decety et al., 2012; Escobar et al., 2014; Treadway et al., 2014). At the neural level, prefrontal and limbic regions impaired in bvFTD (Rosen et al., 2002; Seeley et al., 2008) have been particularly associated with the perception and evaluation of harmful actions (Decety et al., 2008, 2012; Hesse et al., 2015). Specifically, perceiving an individual who intentionally hurts another person triggers an early amygdala boost (Hesse et al., 2015), which plays a critical role in evaluating actual or potential threats (Decety et al., 2008; Phelps, 2006). The OFC is also systematically involved in contextual appraisal and target evaluation in paradigms involving harmful actions (e.g., Decety et al., 2012; Lamm, Batson, & Decety, 2007; Singer et al., 2006). The amygdala and the OFC are strongly connected (Stein et al., 2007) and their effective interactions are critical for decoding emotionally salient information, experiencing empathy, and construing moral judgments (Decety et al., 2008; Saddoris, Gallagher, & Schoenbaum, 2005). Furthermore, observation of an agent who intentionally harms another additionally engages the anterior paracingulate cortex (APC), a region involved in the representation of intentions and social interaction (Akitsuki & Decety, 2009; Decety et al., 2012).

In a recent behavioral study (Baez, Manes, et al., 2014), we assessed a bvFTD sample with a novel paradigm assessing the perception and evaluation of harm to others. The patients presented deficits in intentionality comprehension, empathic concern, and aspects of moral judgment. Nevertheless, empathic concern was the only primary impairment that was neither related nor explained by deficits in executive functions (EFs) or other social cognition domains. Instead, deficits in intentionality comprehension and moral judgment depended on impairments in other domains, such as EFs, emotion recognition, and theory of mind.

To extend these behavioral results, here we investigate whether GM volume in bvFTD patients correlates with their ability to perceive and evaluate harmful actions. Our focus is on their ability to attribute intentionality, assess harmful behavior, show empathic concern, and construe moral judgments. First, we compared the behavioral performance of bvFTD patients and healthy controls on the previously described task. Then, we compared GM volume in both samples using voxel-based morphometry (VBM). Furthermore, we examined the brain regions where atrophy might be associated with specific impairments in bvFTD patients. Finally, we explored whether primary deficits in empathic concern were partially explained by regional GM atrophy, and whether those deficits that seemed to depend on other factors were additionally associated with regional GM atrophy.

2. Methods and materials

2.1. Participants

Twenty-six patients fulfilled the Lund and Manchester criteria (Neary et al., 1998) and the revised criteria for probable bvFTD (Rascovsky et al., 2011). As in previous reports of our group (e.g., Baez, Couto, et al., 2014; Baez et al., 2015; Baez, Manes, et al., 2014; Couto et al., 2013; Garcia-Cordero et al., 2015), diagnosis was made by a group of experts on bvFTD. All patients underwent neurological, neuropsychiatric, neuropsychological, and MRI assessments, and were in an early/mild stage of the disease. Patients with other neurological diseases or psychiatric disorders were excluded.

The performance of bvFTD patients was compared with that of 23 healthy age-, sex-, and education-matched controls without a history of psychiatric or neurological disease (Table 1). All participants provided written informed consent in agreement with the Helsinki declaration. The study was approved by the Ethics Committee of the Institute of Cognitive Neurology.

2.2. Behavioral assessment

The participants' general cognitive status was assessed through the Mini-Mental State Examination (Folstein, Robins, & Helzer, 1983). The MMSE is the most widely applied test to screen for cognitive deficits, and it has been previously employed in the assessment of bvFTD patients (O'Bryant et al., 2008; Osher, Wicklund, Rademaker, Johnson, & Weintraub, 2007). This test assesses orientation, attention, memory, language, and visuospatial abilities. Additionally, all participants were evaluated with the INECO Frontal Screening (IFS) battery (Baez, Ibanez, et al., 2014; Torralva, Roca, Gleichgerrcht, Lopez, & Manes, 2009) (see Table 1). The IFS has been shown to successfully detect executive dysfunction in patients with dementia (Torralva, Roca, Gleichgerrcht, Lopez, et al., 2009). This test includes eight subtests: (1) motor programming (Luria series, "fist, edge, palm"); (2) conflicting instructions (subjects are asked to hit the table once when the administrator hit it twice, or to hit the table twice when the administrator hits it only once); (3) motor inhibitory control; (4) numerical working memory (backward digit span); (5) verbal working memory (months backwards); (6) spatial working memory (modified Corsi tapping test); (7) abstraction capacity (inferring the meaning of proverbs), and (8) verbal inhibitory control (modified Hayling test). The maximum possible score on the IFS is 30 points.

2.2.1. Experimental task (ET)

We used a modified version of a task previously employed to assess bvFTD patients (Baez, Manes, et al., 2014) and a number of neuropsychiatric populations (Baez et al., 2013, 2012). This task evaluates different aspects of intentionality

Table 1 – Demographic data and general cognitive status assessment.

	BvFTD ($n = 26$)	CTR ($n = 23$)	p Value
Demographics			
Age (years)	66.08 (7.45)	62.69 (9.01)	.16
Gender (F:M)	12:14	10:13	.75
Education (years)	15.24 (4.07)	15.65 (2.42)	.67
Cognitive status			
MMSE	25.84 (2.85)	28.26 (2.33)	.002*
IFS Total score	18.25 (5.65)	24.84 (3.67)	.0002*
Motor series	2.44 (.91)	2.65 (.86)	.46
Conflicting instructions	2.68 (.62)	2.76 (.75)	.69
Go- no go	1.76 (1.12)	2.59(.87)	.01*
Backward digits span	3.32 (1.31)	4.18 (1.38)	.04*
Verbal Working memory	1.80 (.50)	1.88 (.33)	.55
Spatial working memory	1.72 (.93)	2.53 (.80)	.006*
Abstraction capacity	1.70 (1.04)	2.64 (.45)	.001*
Verbal inhibitory control	3.00 (2.08)	4.94 (1.02)	.001*

BvFTD = Behavioral variant frontotemporal dementia; MMSE = Minimental State Examination; IFS = INECO Frontal Screening. Asterisks indicate significant differences between groups.

comprehension, empathy, and moral judgment in the context of intentional and accidental harms. The ET 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 msec, respectively. The three following types of situations were depicted: (1) intentional harm, in which one person deliberately inflicts pain on another (e.g., one person purposely steps on someone else's toe); (2) accidental harm, where accidentally inflicts pain on another; and (3) control or neutral situations involving no harm (e.g., one hands a flower to another).

Importantly, since the protagonists' faces were not visible, participants were blind to their facial emotional reactions. However, body expressions and postures provided sufficient information about the victim's emotional reaction and the agent's intention. In this abbreviated version, participants were asked to respond four different questions that effectively reveal empathy impairments in bvFTD (Baez, Manes, et al., 2014) and other neuropsychiatric conditions (Baez et al., 2013, 2012). These questions evaluated: (a) intentionality comprehension (was the action done on purpose?), (b) evaluation of the perpetrator's harmful behavior (how bad was the intention?), (c) empathic concern (how sad do you feel for the victim?), and (d) punishment (how much penalty does this action deserve?). The question about intentionality was answered selecting “Yes” or “No”. The other questions were answered using a computer-based visual analog scale ranging from −9 to 9 —these numbers were not visible to participants. The meaning of the scale extremes depends on the question. For example, in the question “how sad do you feel for the hurt person?”, one extreme of the bar reads “I feel very sad” and the other extreme reads “I don't feel sad at all”. We measured accuracy for the intentionality question and ratings and raw reaction times (RTs) for the other questions. RTs measurements indicated the lapse between presentation of the question and the participant's response. Before testing, to ensure correct understanding of the instructions, we administered a shorter training version of the task involving similar situations.

2.3. MRI scanning

Participants were scanned in a 1.5 T Phillips Intera scanner equipped with a standard head coil. A T1-weighted spin echo sequence was used to generate 120 contiguous axial slices (TR = 2300 msec; TE = 13 msec; flip angle = 68°; FOV = 256 × 256 mm; matrix size = 256 × 240; in-plane resolution = 1 × 1 mm; slice thickness = 1 mm).

2.4. Data analysis

2.4.1. Behavioral data

We compared demographic and neuropsychological data between samples using ANOVA tests; categorical variables were analyzed through X^2 tests. The ratings and RTs for each question were analyzed independently using a 2 (group: bvFTD *vs* controls) × 3 (condition: intentional, accidental, neutral) factorial ANOVA. When a significant interaction between group and condition was found, we examined between-group differences in ratings or RTs using the Tukey's HSD post-hoc test. Intra-group comparisons were also conducted via repeated measures ANOVA. Differences among conditions (intentional harm, accidental harm, and neutral situations) were examined with Tukey's HSD post-hoc tests. Given that working memory has been particularly associated with empathy (Ze, Thoma, & Suchan, 2014) and mentalizing skills (Gordon & Olson, 1998), we re-analyzed intentionality comprehension and empathic concern data covarying for backward digit span and spatial working memory scores. Effect sizes were calculated through partial eta (η^2) tests. The statistical significance level was set at $p < .05$.

2.4.2. VBM analysis

Images were preprocessed using the DARTEL Toolbox, in accordance with previously described procedures (Ashburner & Friston, 2000). Then, modulated 12-mm full-width half-maximum kernel-smoothed (Good et al., 2001) images were normalized to the MNI space and analyzed through general linear models for 2nd level analyses on SPM-8 software. To explore regional GM reduction in the bvFTD group relative to controls, we performed a two-sample comparison, including total intracranial volume as a confounding covariate ($p < .05$, FWE corrected at cluster level, extent threshold = 100 voxels).

2.4.3. Relationship between atrophic brain regions and specific impairments in bvFTD patients

In the bvFTD group, we performed seven multiple regression analyses in SPM-8 to identify atrophied brain regions that were associated with impaired performance on the ET (one for each measure showing significant differences between patients and controls: (1) intentionality comprehension of accidental harms, harmful behavior ratings for (2) neutral and (3) intentional harms, empathic concern for (4) neutral and (5) intentional harms, and punishment ratings for (6) neutral and (7) intentional harms). In order to explore the relationship between regional GM reduction and the deficits observed in bvFTD patients, these analyses were restricted to areas of significant GM atrophy in patients relative to controls. Age and total intracranial volume were included as covariates of no interest ($p < .05$ uncorrected, extend threshold = 50 voxels).

2.4.4. Other factors related to intentionality and empathic concern impairments in bvFTD patients

Finally, using SPSS 22.0, we conducted multiple regression analyses to explore whether impairments in the two ET measures associated with reduced GM volumes (as evidenced by the previous regression analyses) were partially explained by (a) GM volume in areas related with ET performance, or (b) other relevant factors, such as EFs or sex. We estimated two different models in which the measures significantly associated with GM reductions in the bvFTD group were separately considered as dependent variables. The first model included intentionality comprehension of accidental harms as the dependent variable. In the second one, the dependent variable consisted in empathic concern ratings for intentional harms. The predictors in the first and the second models were GM volume values from the clusters significantly associated with (i) intentionality comprehension of accidental harms and (ii) empathic concern for intentional harms, respectively. In addition, the variables of group, sex, and total IFS score were included as predictors in both models. Sex was included as a predictor since several studies (e.g., Baron-Cohen & Wheelwright, 2004; Preis & Kroener-Herwig, 2012; Toussaint & Webb, 2005) have reported higher empathy levels in women than men. The IFS was selected as a predictor because it includes several EFs subtests, which robustly detect executive dysfunction in bvFTD (Torralva, Roca, Gleichgerrcht, Lopez, et al., 2009). Both patients and controls were included in these regression analyses. The statistical significance level was set at $p < .05$.

3. Results

3.1. Behavioral data

Demographic and neuropsychological data is shown in Table 1. Behavioral results are summarized in Fig. 1.

Regarding intentionality comprehension, we observed a significant interaction between group and condition [F (2, 94) = 5.88, $p < .01$, $\eta^2 = .18$]. A post-hoc analysis (Tukey's HSD, $MS = 640.70$, $df = 140.96$) revealed lower comprehension of the intentionality of accidental harms in patients than in controls ($p < .01$). Group differences in intentionality comprehension for accidental harm remained significant after adjusting for working memory [$F(1, 44) = 4.41$, $p < .05$, $\eta^2 = .11$]. Backward digit span ($p = .30$) or spatial working memory ($p = .13$) did not show a significant effect on intentionality comprehension. In patients, intra-group comparisons via repeated-measures ANOVA showed significant differences in the intentionality comprehension among the three conditions [$F(2, 48) = 12.21$, $p < .001$, $\eta^2 = .33$]. A post-hoc comparison (Tukey HSD, $MS = 821.60$, $df = 48$) revealed that intentionality comprehension of intentional ($p < .001$) and neutral situations ($p < .001$) was higher than the comprehension of accidental harms. In controls, there were no significant differences among the three conditions [$F(2, 44) = .99$, $p = .37$, $\eta^2 = .04$].

Furthermore, a significant interaction between group and condition was observed in ratings of harmful behavior [F (2, 94) = 11.27, $p < .01$, $\eta^2 = .19$]. A post-hoc analysis (Tukey HSD, $MS = 12.01$, $df = 117.50$) showed that patients had higher ratings than controls for neutral ($p < .01$) and accidental ($p < .05$) situations. Intra-group comparisons showed significant differences in harmful behavior ratings among the three conditions in both patients [$F(2, 48) = 45.83$, $p < .001$, $\eta^2 = .67$] and controls [$F(2, 44) = 126.92$, $p < .001$, $\eta^2 = .85$]. Post-hoc comparisons [patients:(Tukey's HSD, $MS = 7.58$, $df = 48$), controls: (Tukey's HSD, $MS = 8.02$, $df = 44$)] revealed that, in both groups, intention-to-harm ratings were higher for intentional harm than for neutral ($p < .001$) and accidental ($p < .001$) situations. Furthermore, in both groups harmful behavior ratings for accidental harm were higher than for neutral situations ($p < .001$).

We also found a significant interaction between group and condition in empathic concern ratings [F (2, 94) = 21.04, $p < .01$, $\eta^2 = .18$]. A post-hoc analysis (Tukey HSD, $MS = 12.29$, $df = 107.74$) revealed that patients rated intentional harms lower ($p < .05$) and neutral situations higher ($p < .01$) than controls. Between-group differences in ratings of empathic concern for intentional harm remained significant after adjusting for working memory [$F(1,44) = 17.82$, $p < .001$, $\eta^2 = .33$]. Backward digit span ($p = .29$) or spatial working memory ($p = .79$) had no significant effect on empathic concern. Intra-group comparisons showed significant differences in empathic concern ratings among the three conditions in both patients [$F(2,48) = 32.54$, $p < .001$, $\eta^2 = .57$] and controls [$F(2, 44) = 146.62$, $p < .001$, $\eta^2 = .86$]. Post-hoc comparisons [patients: (Tukey's HSD, $MS = 8.15$, $df = 48$), controls:

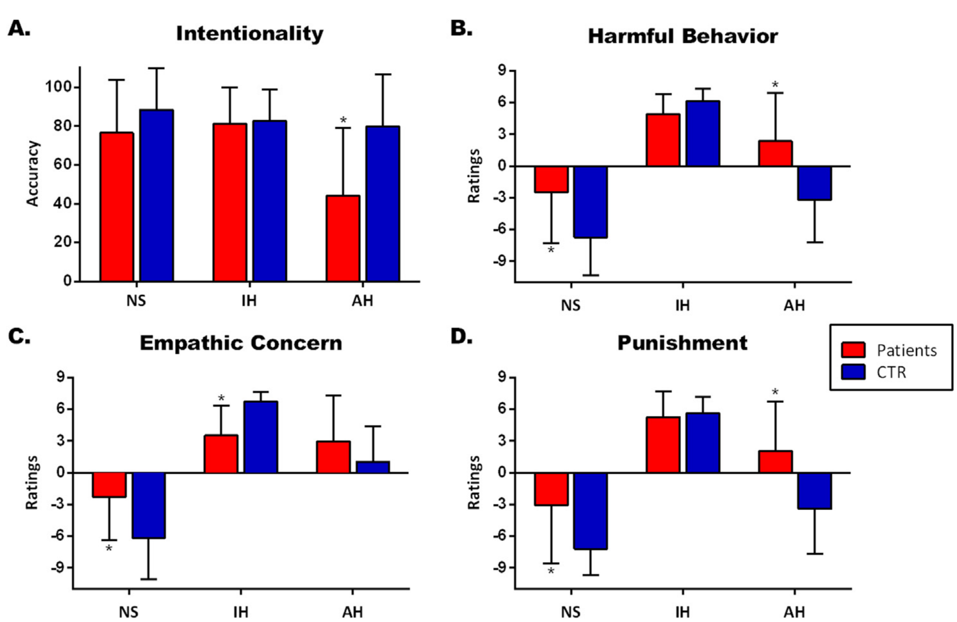

Fig. 1 – Behavioral results during the evaluation of harmful actions. Significant differences between groups are indicated by * (A) Intentionality comprehension accuracy; (B) Harmful behavior ratings; (C) Empathic concern ratings; (D) Punishment ratings. NS = neutral situations, IH = intentional harms, AH = accidental harms.

(Tukey's HSD, $MS = 6.53$, $df = 44$)] revealed that in both groups empathic concern ratings for intentional and accidental harm were higher than for neutral situations ($p < .001$). In controls, empathic concern ratings for intentional harm were higher than for accidental harm ($p < .001$). This difference was not observed in bvFTD patients.

There was also a significant interaction between group and condition [F (2, 94) = 12.50, $p < .01$, $\eta^2 = .21$] in punishment ratings. A post-hoc analysis (Tukey's HSD, $MS = 14.61$, $df = 103.94$) showed that patients rated neutral ($p < .01$) and accidental ($p < .01$) situations higher than controls. Intragroup comparisons revealed significant differences in punishment ratings among the three conditions in both patients [$F(2, 48) = 42.86$, $p < .001$, $\eta^2 = .64$] and controls [$F(2, 44) = 159.02$, $p < .001$, $\eta^2 = .87$]. Post-hoc comparisons [patients: (Tukey's HSD, $MS = 10.65$, $df = 48$), controls: (Tukey's HSD, $MS = 6.28$, $df = 44$)] revealed that in both groups punishment ratings were higher for intentional harm than for neutral ($p < .001$) and accidental ($p < .001$) situations. Furthermore, in both groups punishment ratings for accidental harm were higher than for neutral situations ($p < .001$).

No RT differences were observed between groups. Means and standard deviations are shown in supplementary material (Table S1).

3.2. *VBM results*

3.2.1. *BvFTD brain atrophy*

Relative to controls, bvFTD patients exhibited an atrophy pattern similar to those reported in previous studies (Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009; Rosen et al., 2002; Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Whitwell et al., 2009) (see Fig. 2 and Table 2). One cluster located in the frontal lobes included the bilateral OFC and the right ventromedial prefrontal cortex, and extended to the right insula and the right ACC. Moreover, two clusters of significant GM reduction were found in the left and right temporal lobes, respectively. The first cluster included the left inferior temporal gyrus and extended to the fusiform gyrus. The second cluster comprised voxels in the right amygdala, the hippocampus, and the parahippocampal gyrus.

3.2.2. *Atrophied brain regions related to specific impairments in bvFTD patients*

In the bvFTD group, we performed seven multiple regression analyses to identify atrophied brain regions that were associated with impaired performance on the ET (one for each measure showing significant differences between patients and controls). In bvFTD patients, lower accuracy in intentionality comprehension was positively associated with lower GM volumes in two clusters, involving limbic structures, such as the right amygdala (extending to the hippocampus), and the APC (Fig. 3A). Furthermore, lower empathic concern was positively associated with decreased GM volumes in the left OFC (gyrus rectus) (Fig. 3A). No significant associations were found between ratings of harmful behavior, empathic concern or punishment for neutral or accidental situations and atrophied brain regions. In summary, in bvFTD patients lower intentionality comprehension for accidental harms was associated with greater atrophy in the right amygdala and the APC. Lower empathic concern was associated with greater atrophy in the left OFC.

3.2.3. *Are impairments in intentionality and empathic concern partially explained by GM volume in atrophied brain areas?*

We conducted two additional multiple regression analyses. First, we explored whether GM volumes in the regions associated with ET impairments were enough to explain impairments in intentionality comprehension for accidental harm and empathic concern for intentional harm (the only two measures associated with atrophied areas). Second, we

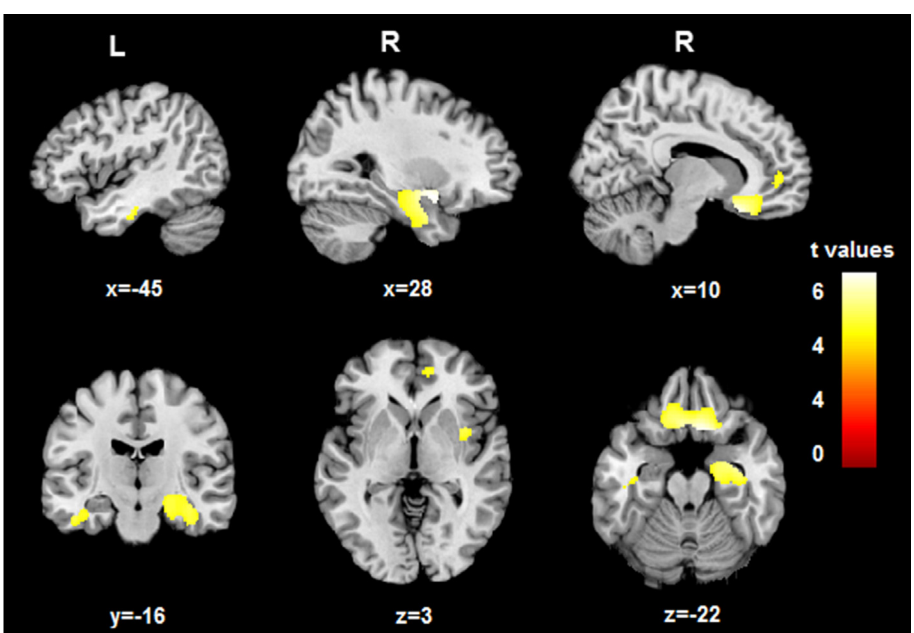

Fig. 2 – Regions of significant GM volume loss in the bvFTD group compared with the control group ($p < .05$, FWE-corrected).

Table 2 – Regions of significant atrophy in bvFTD patients compared with controls.

Region	Cluster k	x	y	z	Peak t	Peak z
Rigth amygdala	3045	28	4	−16	6.88	5.67
Right hippocampus		34	−7	−24	6.24	5.28
Right parahippocampal gyrus		28	1	−30	5.87	5.04
Right gyrus rectus	3177	10	19	−22	6.81	5.63
Right middle frontal gyrus, orbital part		13	46	−3	5.12	4.53
Right anterior cingulate cortex		4	43	12	4.78	4.28
Left inferior temporal gyrus	290	−45	−16	−27	5.42	4.74
Left middle temporal lobe		−36	−3	−18	4.76	4.27

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

assessed whether other relevant factors, such as EFs or sex, were also associated with these impairments. A first model including intentionality for accidental harms as the dependent variable [F (5, 43) = 6.01, $p < .01$] showed that executive functioning (beta = .35) and group (beta = .31) predicted comprehension of intentionality behind accidental harms, explaining 41% of the variance. Thus, higher accuracy in intentionality comprehension was associated with higher executive functioning and with control group membership. We carried out a second model with empathic concern for intentional harms as the dependent variable (Fig. 3B). This model [F (4, 43) = 10.26, $p < .01$] evidenced that GM volume in the left OFC (beta = .31) and group (beta = .61) was significantly associated with empathic concern ratings, explaining 69% of the variance. This indicates that higher empathic concern was associated to larger GM volume in the OFC and with control group membership. Standardized coefficients are shown in Table 3.

4. Discussion

This is the first study investigating the relationship between regional GM reduction in bvFTD patients and different aspects involved in the evaluation of intentional harm. Furthermore, we explored whether intentionality comprehension and empathic concern deficits in bvFTD patients were partially explained by regional GM atrophy or by executive dysfunction. Results showed that difficulties to assess intentionality in accidental harms were associated with lower GM volumes in limbic structures (amygdala and APC). Moreover, deficits in empathic concern were associated with atrophy of the left OFC. Impairments in harmful behavior and punishment ratings for neutral and accidental situations were not associated with GM volume in atrophied brain regions. Additionally, deficits in empathic concern were partially explained by atrophy of the OFC but not by EFs. Conversely, impairments in intentionality comprehension were predicted by EFs but not by specific regional atrophy. These results provide further evidence of a primary deficit in empathic concern in bvFTD associated with a key early region of atrophy. The identification of primary empathy impairments and their relationship with the atrophy pattern of bvFTD patients may be useful to establish behavioral patterns and to predict disease progression.

4.1. *Behavioral results*

We replicated the findings of a recent behavioral study in bvFTD patients (Baez, Manes, et al., 2014). Regarding

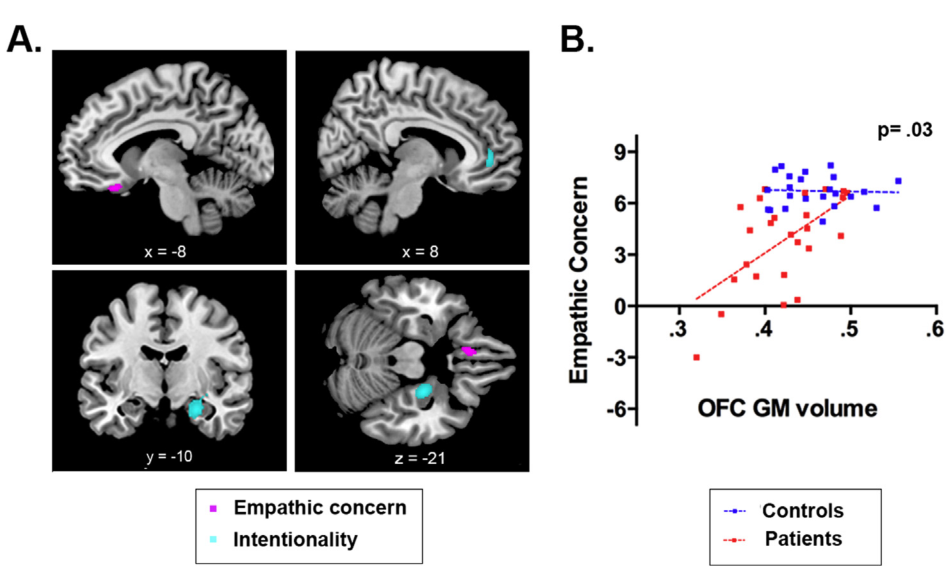

Fig. 3 – Atrophied brain regions related to behavioral impairments in bvFTD patients. (A) Regions of reduced GM volume associated with intentionality comprehension of accidental harms and empathic concern for intentional harms; (B) Significant associations between GM volume in the left OFC and ratings of empathic concern for intentional harms.

Table 3 – Standardized coefficients of the multiple regression models.

Predictors	Model I DV: Intentionality		Model II DV: Empathic concern	
	β	p	β	p
Group	.31	.04	.61	.001
Gender	.19	.17	.04	.76
IFS total score	.35	.02	−.22	.13
Right amygdala GMV	.08	.66		
Right paracingulate cortex GMV	−.04	.80		
Left gyrus rectus GMV			.31	.03

DV = dependent variable; IFS = INECO frontal screening; GMV = gray matter volume.

intentionality comprehension, patients showed difficulties in distinguishing accidental from neutral and intentional harms. This is consistent with previous demonstrations that bvFTD patients cannot normally infer the intentionality behind others' actions (Cerami et al., 2014; Gregory et al., 2002; Poletti, Enrici, & Adenzato, 2012; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009) or understand ambiguous emotional scenes (Fernandez-Duque, Hodges, Baird, & Black, 2010). Contextual cues help to bias the intrinsic meaning of ambiguous targets (Amoruso et al., 2014; Bar, 2004), particularly in the interpretation of harmful actions (Melloni, Lopez, & Ibanez, 2013) and other social cognition skills (Ibanez, Kotz, Barrett, Moll, & Ruz, 2014; Ibanez & Manes, 2012). In line with a previous study in healthy subjects (Decety et al., 2012), the results of intra-group analyses showed that comprehension of intentionality was higher for intentional than accidental harm. This suggests that situations of the latter kind are less clear and explicit, thus increasing the level of ambiguity and the demands in the attribution of intentionality.

In addition, patients rated the harmful behavior for neutral and accidental situations higher than controls. Intentionality detection is a decisive step in determining whether an action is malicious (Decety et al., 2012). Inability to infer the intentions of others' actions may affect harmful behavior ratings. Moreover, patients with bvFTD tend to overattribute bad intentions to the agent (Gregory et al., 2002; Kipps & Hodges, 2006), even if the action was unintentional.

Compared to controls, bvFTD patients showed higher empathic concern ratings for neutral situations. However, in neutral situations nobody is being hurt, which suggests that the patients misinterpreted these scenarios and provided unexpected empathic concern ratings. In addition, we found that patients showed lower empathic concern ratings for intentional harm. In agreement with these results, intra-group comparisons showed that, unlike bvFTD patients, controls provided higher empathic concern ratings for intentional than accidental harm. Supporting our results, previous studies (Eslinger et al., 2011; Lough et al., 2006; Rankin et al., 2006) have reported diminished levels of empathic concern in bvFTD as rated by relatives or caregivers.

Regarding aspects related to moral judgment, patients gave higher punishment ratings to neutral and accidental situations than controls. However, neutral situations did not represent a wrong action and accidental harms may go unpunished, regardless of their magnitude (Treadway et al., 2014; Young & Saxe, 2009). Thus, these findings again suggest deficits in inferring the intentionality of the action and in attributing bad intentions even when this was not the purpose. Moral reasoning relies on both affective and cognitive processes to integrate intentions and action consequences (Decety et al., 2012). In agreement with previous reports (Baez, Couto, et al., 2014; Lough et al., 2006; Mendez, 2006; Mendez, Anderson, & Shapira, 2005), our results suggest that such aspects of moral reasoning are impaired in bvFTD.

4.2. *Relationship between GM volume and intentionality comprehension and empathy impairments in bvFTD patients*

Consistent with previous reports (Rosen et al., 2002; Seeley et al., 2009), our results showed that bvFTD patients exhibited the classically reported atrophy pattern involving the frontal (ventromedial prefrontal, orbitofrontal, and cingulate cortices), insular, and temporal (parahippocampal, fusiform gyri, amygdala and hippocampus) lobes.

Multiple regression analysis revealed that impairments in comprehension of intentionality behind accidental harm were associated with lower GM volumes in limbic structures, such as the amygdala and the APC, although this ability is also associated to EFs (see below). The amygdala plays a critical role in detecting intentional harm in social contexts (Hesse et al., 2015) and in the emotional assessment of morally salient scenarios (Shenhav & Greene, 2014). In line with these results, multiple regression analysis revealed that impairments in comprehension of intentionality behind accidental harm were associated with lower GM volumes in limbic structures, such as the amygdala and the APC. Moreover, the amygdala is the only structure which discriminates between intentional and accidental harm in an early time window (<200 msec) and predicts their classification as intentional or unintentional (Hesse et al., 2015). Furthermore, our results are coherent with those of a previous study in bvFTD (Eslinger et al., 2011) showing that changes in cognitive empathy (as rated by caregivers) are related to atrophy in the right dorsolateral prefrontal cortex, the left caudate, and the right amygdala. In addition, the cognitive aspects of empathy have been associated to mentalizing (Zaki & Ochsner, 2012), a fundamental ability to empathize with others by considering their mental states. This ability is compromised subsequent to amygdala damage (Fine, Lumsden, & Blair, 2001; Stone, Baron-Cohen, Calder, Keane, & Young, 2003). The APC is also a key region for mentalizing (Gallagher & Frith, 2003; Walter, Abler, Ciaramidaro, & Erk, 2005; Walter et al., 2004). Specifically, the APC is implicated in the representation of intentions of an agent involved in social interaction, regardless of whether this interaction is observed or imagined (Walter et al., 2005, 2004). Thus, our results align with previous evidence implicating the amygdala and the APC in the perception of harm and in the inference of intentionality of others' actions.

Also, in bvFTD patients, impairments in empathic concern for intentional harms were associated with decreased GM volumes in the OFC (gyrus rectus). According with present results, contextual appraisal and target evaluation in empathy-for-pain paradigms predominantly activate the OFC, among other areas (e.g., Decety et al., 2012; Lamm et al., 2007; Singer et al., 2006). Traditionally, the OFC has been implicated in processing information concerning rewards and punishments, and in integrating cognitive process with affective values (Amodio & Frith, 2006). The interplay between basic affective mechanisms and higher order computations in the OFC plays a crucial role in the experience of empathy and feeling concern for others (Decety, Skelly, & Kiehl, 2013; Viskontas, Possin, & Miller, 2007). Moreover, the association between atrophy and empathic concern deficits in bvFTD patients is consistent with lesion studies (e.g., Hornak et al., 2003; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004) showing that individuals with circumscribed OFC damage are impaired in both cognitive and affective aspects of empathy. Our results are also in line with a previous study in bvFTD patients (Rankin et al., 2006) showing that empathy scores (as rated by caregivers) significantly correlated with GM volumes in the right temporal pole, the right fusiform gyrus, and the right OFC. Thus, our present findings and previous evidence suggest that the OFC is a relevant region in perceiving and evaluating harmful actions to others, and that atrophy in this area may impair affective aspects of empathy, such as empathic concern.

We found no significant correlations between GM volume in atrophied brain regions and harmful behavior, empathic concern or punishment ratings for neutral or accidental situations. These three aspects are strongly dependent on the observer's interpretation of intention behind a harmful action. As shown elsewhere (Baez, Manes, et al., 2014; Gregory et al., 2002; Kipps & Hodges, 2006), bvFTD patients have difficulties in understanding the intentionality of others' actions, tending to overattribute bad intention even when this was not the purpose. Thus, deficits in intentionality comprehension may affect the ratings of these aspects. Moreover, in agreement with previous results (Baez, Manes, et al., 2014), our findings suggest that these impairments may be secondary to deficits in other domains that are also affected in bvFTD such as EFs, emotion recognition, and theory of mind.

We performed additional multiple regression analyses to explore whether intentionality comprehension and empathic concern impairments were partially explained by (a) reduced GM volumes in areas associated with task performance or (b) other relevant factors, such as EFs or sex. Comprehension of intentionality behind accidental harm was predicted by EFs, but not by atrophy of amygdala or APC. This finding is consistent with the results of our previous behavioral study in bvFTD (Baez, Manes, et al., 2014) suggesting that deficits in intentionality comprehension are explained by EFs impairments. Moreover, these results are in line with studies in healthy adults (Ahmed & Stephen Miller, 2011; Carlson & Moses, 2001) and clinical populations (Aboulafia-Brakha, Christe, Martory, & Annoni, 2011; Fisher & Happe, 2005) suggesting that the ability to infer mental states is linked to EFs. Specifically, working memory (Gordon & Olson, 1998), inhibitory control (Carlson & Moses, 2001), problem solving (Ahmed & Stephen Miller, 2011), and phonological fluency (Ahmed & Stephen Miller, 2011) are associated with mentalizing abilities. Inferring the intentions of others requires the inhibition of one's own perspective (Ruby & Decety, 2003; Samson, Apperly, Kathirgamanathan, & Humphreys, 2005). Furthermore, although working memory and intentionality comprehension deficits seem to be independent in the bvFTD group, the former domain is required to hold and manipulate cues from multiple sources of input, particularly in more complex social situations (Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012). During the ET, accidental harm scenarios are less clear and explicit. Therefore, accurate recognition of these situations may involve greater working memory and inhibitory control demands. Further studies in bvFTD should assess the contribution of working memory and other EFs to mentalizing abilities using tasks specifically designed to evaluate the inference of others' intentions.

When EFs were introduced in a multiple regression model, a lack of association between intentionality and GM volumes was observed. This suggests that although limbic regions are relevant to the inference of intentionality (Akitsuki & Decety, 2009; Decety et al., 2012; Gallagher & Frith, 2003; Walter et al., 2004), EFs seem to be a stronger predictor of this ability. Importantly, both EFs and intentionality have been also related to fronto-limbic structures, including amygdala, ACC, and prefrontal cortex (Carter et al., 2000; Cohen et al., 2015; Li et al., 2012; Robbins, 2007). Thus, results suggest that behavioral and anatomical measures of EFs are related to intentionality.

Empathic concern deficits were predicted by orbitofrontal atrophy, but no by EFs. Furthermore, covariance analyses revealed that neither verbal nor spatial working memory performance is related to empathic concern impairments. Thus, our results suggest that empathic concern is the only component primarily affected in bvFTD that is neither related to nor explained by EFs, emotion recognition, theory of mind, or general cognitive status.

Taken together, our present and previous results indicate that empathic concern is intrinsically affected in bvFTD and that such deficits are partially explained by orbitofrontal atrophy. This brain region is one of the first to show atrophy in bvFTD (Perry et al., 2006). Thus, the early atrophy of the OFC seems to be closely related with primary empathic concern deficits observed in bvFTD patients.

4.3. *Implications and conclusions*

This is the first examination of the relationship between GM atrophy in bvFTD patients and the evaluation of intentional harm. In these patients, atrophy of limbic structures (amygdala and APC) was related to impairments in intentionality comprehension, while atrophy of the OFC was associated with empathic concern deficits. However, only atrophy of the OFC predicted deficits in empathic concern. Intentionality comprehension impairments were predicted by EFs. Thus, although the perception and evaluation of harmful actions are variously compromised in bvFTD, deficits in empathic concern may be central to this syndrome as they are associated with the earliest atrophied region. Impairments in empathic concern may be the core of empathy deficits systematically observed in these patients. Moreover, our results suggest that adequate executive functioning and preserved GM volume in the amygdala and the APC are relevant to comprehend the intentionality, while GM integrity in the OFC is crucial for feeling empathic concern for others.

Some limitations of this study should be mentioned. Although we used a somewhat liberal significance level for some of the VBM multiple regressions, we controlled for age and total intracranial volume and ruled them out as confounds. Moreover, given our moderate sample size, more subtle associations may have been missed due to low statistical power. While our sample size is large enough for the multiple regression analyses performed (Green, 1991; Stevens, 2002; Tabachnick & Fidell, 1989), further studies should assess the structural correlates of intentionality comprehension and empathic concern in larger groups.

One of the strengths of the current study is its reliance on a more ecological design that circumvents some limitations of self-report questionnaires. The task employed here detected deficits in intentionality comprehension, empathy, and moral judgment. These results emphasize the value of tasks involving real-life social scenarios (Burgess, Alderman, Volle, Benoit, & Gilbert, 2009; Ibanez & Manes, 2012; Torralva, Roca, Gleichgerrcht, Bekinschtein, et al., 2009), as evidenced by their greater sensitivity in the clinical assessment of neuropsychiatric populations. From a clinical perspective, given that adequate empathic functioning is an important element of higher social functioning (Rankin et al., 2005), primary empathy impairments should be considered in the assessment and early treatment of bvFTD.

In conclusion, our study highlights the importance of limbic structures in comprehending intentionality and, more particularly, of the OFC in the early empathy changes observed in bvFTD. Longitudinal studies are needed to test whether atrophy of this brain region may predict disease progression based on empathic concern levels. Moreover, future studies should explore the relationship between the atrophy pattern and different aspects of the evaluation of harmful actions in other variants of frontotemporal dementia. A more subtle understanding of these complex social cognitive deficits in bvFTD will improve assessment in clinical settings. Furthermore, insights into relevant factors contributing to social impairments in bvFTD patients may shed light on potential strategies for early diagnosis and for the development of cognitive stimulation programs.

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Supplementary data

Supplementary data related to this article can be found at doi:10.1016/j.cortex.2015.11.007.

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