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Integration of Intention and Outcome for Moral Judgment in Frontotemporal Dementia: Brain Structural Signatures

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Key Words

Moral judgment · Behavioral variant of frontotemporal dementia · Magnetic resonance imaging · Voxel-based morphometry · Structural correlates

Abstract

Background: Moral judgment has been proposed to rely on a distributed brain network. This function is impaired in behavioral variant frontotemporal dementia (bvFTD), a condition involving damage to some regions of this network. However, no studies have investigated moral judgment in bvFTD via structural neuroimaging. ***Methods:*** We compared the performance of 21 bvFTD patients and 19 controls on a moral judgment task involving scenarios that discriminate between the contributions of intentions and outcomes. Voxel-based morphometry was used to assess (a) the atrophy pattern in bvFTD patients, (b) associations between gray matter (GM) volume and moral judgments, and (c) structural differences between bvFTD subgroups (patients with relatively preserved moral judgment and patients with severer moral judgment impairments). ***Results:*** Patients judged attempted harm as more permissible and accidental harm as less permissible than controls. The groups' performance on accidental harm was associated with GM volume in the precuneus. In controls, it was also associated with the ventromedial prefrontal cortex (VMPFC). Also, both groups' performance on attempted harm was associated with GM volume in the temporoparietal junction. Patients exhibiting worse performance displayed smaller GM volumes in the precuneus and temporal pole. ***Conclusions:*** Results suggest that moral judgment ab-

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normalities in bvFTD are associated with impaired integration of intentions and outcomes, which depends on an extended brain network. In bvFTD, moral judgment seems to critically depend on areas beyond the VMPFC.

Introduction

Current theoretical models [1–3] have suggested that high-level social processes, such as moral judgment, may be better understood in terms of extended cortical-limbic networks. Previous functional magnetic resonance imaging (MRI) studies [4–8] have identified a distributed brain network commonly engaged by moral cognition tasks. This network includes the ventromedial prefrontal cortex (VMPFC), the orbitofrontal cortex, the ventrolateral prefrontal cortex, the amygdala, the superior temporal sulcus, the precuneus, and the temporoparietal junction (TPJ). Specifically, the VMPFC seems to play multiple roles in social cognitive processes; for example, it biases moral judgment by associating external stimuli with socioemotional value and is involved in theory of mind and empathy [9, 10]. The orbitofrontal and ventrolateral prefrontal cortices are implied in the inhibition of automatic or impulsive responses and in processing social prompts [11, 12]. The amygdala is involved in moral learning and threat responses [13–15]. The precuneus subserves processing of mental states [16] and integration of self-referential stimuli in the broader emotional or moral context of the self [17]. Finally, the TPJ is involved in the inference of mental states [18] and the integration of information from several sources to establish a social context for decision-making [19].

Although this moral judgment network has been systematically identified, the VMPFC has received particular attention and has been proposed as a critical region for processing intention and outcome information during moral judgments [20–22]. Patients with VMPFC damage judge harmful intentions in the absence of harmful outcomes as more permissible than healthy subjects [21]. Thus, while several regions play a fundamental role in moral cognition, the VMPFC proves critical in judging moral situations.

In line with the network models, a recent study [23] demonstrated similar impairments in integrating intention and outcome information for moral judgment in patients with prefrontal lesions either with or without VMPFC damage, as well as in behavioral variant frontotemporal dementia (bvFTD) patients. Although the VMPFC may be affected in bvFTD patients, their atrophy pattern extends to other frontotemporal areas. Previous studies [24–27] have shown that atrophy in bvFTD also involves the orbitofrontal cortex, the cingulate cortex, the amygdala, the insula, and the right temporal pole (TP). This widespread atrophy pattern suggests that a more diffuse and extended network may be involved in moral judgment.

The processing of intentions and outcomes is crucial for moral judgment, but no study on bvFTD has yet investigated the issue via structural neuroimaging. This study is the first to report gray matter (GM) changes associated with moral judgments in bvFTD patients and controls. First, we compared the behavioral performance of both groups on a well-characterized task [21, 23] involving scenarios that separate the contributions of intentions and outcomes to moral judgment. Then, we performed voxel-based morphometry (VBM) to measure and compare GM volumes in bvFTD patients and controls. Furthermore, we explored the association between GM volumes and moral judgments in each group. Finally, we examined the structural anatomical differences between the bvFTD subgroups exhibiting low and intermediate performance on the moral judgment task. We expected bvFTD patients to show deficits in integrating intentions and outcomes for moral judgment. We further predicted that these impairments would be associated with GM volume in atrophied regions. Finally, we hypothesized that GM volume in regions beyond the VMPFC would be associated with moral judgment in both groups.

Materials and Methods

Participants

Twenty-one patients fulfilled the revised criteria for probable bvFTD [28]. As in previous reports by our group [29–32], diagnosis was initially made by a group of experts in bvFTD. Each case was individually reviewed in a multidisciplinary clinical meeting involving cognitive neurologists, psychiatrists, and neuropsychologists. bvFTD patients were recruited as part of a broader ongoing study on frontotemporal dementia [23, 29, 33, 34]. Patients presented with functional impairment and prominent changes in personality and social behavior as verified by a caregiver during initial assessment. All patients underwent a standard examination battery including neurological, neuropsychiatric, and neuropsychological examinations and a clinical MRI scan. Patients were included only if they showed frontal or temporal atrophy on MRI. Patients with white matter abnormalities were excluded. All patients were in early/mild stages of the disease and did not meet criteria for specific psychiatric disorders, as assessed by psychiatric examination. Patients presenting primarily with language deficits were excluded.

The performance of bvFTD patients was compared with that of 19 healthy controls. By using a groupwise matching criterion, control subjects were paired one by one (considering a specific range) with the bvFTD patients. Matching criteria were sex, age (±4 years), and years of education (±4 years; table 1a). Control subjects were recruited from a larger pool of volunteers who did not have a history of drug abuse or a family history of neurodegenerative or psychiatric disorders. All of the participants provided written informed consent in accordance with the Helsinki Declaration. The Ethics Committee of the Institute of Cognitive Neurology approved this study.

Behavioral Assessment

The general cognitive status of the participants (table 1) was assessed using the Mini-Mental State Examination (MMSE) [35] and the INECO Frontal Screening [31].

Moral Judgment Task

According to a protocol reported elsewhere [21, 23], we presented the participants with 24 scenarios. Four variations of each scenario followed a 2 × 2 design: (1) the protagonists either harmed another person (negative outcome) or did no harm (neutral outcome); (2) the protagonists either believed that they would cause harm (negative intention) or believed that they would cause no harm (neutral intention; fig. 1). Each possible belief was true for one outcome and false for the other outcome. Thus, the 4 scenarios were (1) no harm, (2) accidental harm, (3) attempted harm and (4) successfully attempted harm (fig. 1). After reading each story, the participants were asked to rate the scenario on a Likert scale ranging from totally permissible (7) to totally forbidden (1).

The participants were shown 24 scenarios, comprising 6 trials of each of the 4 conditions. The stimuli were presented in pseudorandom order, and the conditions were counterbalanced across participants. The entire text remained visible throughout each trial, to decrease the working memory load. The total duration of the task was about 20–25 min. All patients successfully completed the 24 trials. The original set of scenarios [21] is provided in the supplementary material (see www.karger.com/doi/10.1159/000441918 for all suppl. material).

MRI Scanning

All participants were scanned using a 1.5-tesla Phillips Intera scanner equipped with a standard head coil. A T1-weighted spin echo sequence was used to generate 120 contiguous axial slices (TR = 2,300 ms; TE = 13 ms; flip angle = 68°; FOV = rectangular 256 mm; matrix size = 256 × 240; slice thickness = 1 mm).

Data Analysis

Behavioral Data

Demographic and neuropsychological data were compared using ANOVA and χ^2 tests for the categorical variables. The assumption of normality was verified using the Shapiro-Wilk test. The moral judgments were analyzed using a mixed ANOVA. Planned comparisons were performed using one-way ANOVA. To control for the influence of the general cognitive state on the moral judgments, we applied an ANCOVA test adjusted for MMSE scores. We reported only effects that were still significant after covariation. Paired-sample t tests were used to compare intragroup performance on the conditions in which the patients differed from controls.

Table 1. Demographic data, general cognitive status assessment and single-case comparisons

a Demographic data and general cognitive status assessment

	bvFTD (n = 21)	Controls (n = 19)	p
Demographics			
Age, years	63.80 (7.33)	60.42 (6.77)	0.14
Gender (F/M)	10/11	10/9	0.75
Education, years	14.23 (4.09)	15.21 (3.82)	0.44
Cognitive status			
MMSE	25.47 (3.47)	28.89 (1.28)	0.0002
IFS total score	16.38 (7.03)	24.99 (2.28)	0.00001

b Single-case analyses comparing the moral global score of each bvFTD patient to the scores obtained by the control group

	Moral global score	t	p
IMJ bvFTD subgroup			
Subject 1	4.5	2.41	0.01
Subject 2	4.3	2.20	0.02
Subject 3	4.2	2.09	0.02
Subject 4	5.5	3.45	0.001
Subject 5	4.7	2.62	0.008
Subject 6	5.0	2.93	0.004
Subject 7	4.3	2.20	0.02
Subject 8	3.8	1.67	0.05
Subject 9	5.2	3.14	0.002
Subject 10	3.8	1.67	0.05
Subject 11	4.2	2.09	0.02
PMJ bvFTD subgroup			
Subject 12	2.0	0.2	0.41
Subject 13	3.0	0.83	0.20
Subject 14	3.3	1.15	0.13
Subject 15	2.0	0.2	0.41
Subject 16	3.7	1.5	0.06
Subject 17	3.7	1.5	0.06
Subject 18	2.8	2.2	0.26
Subject 19	3.3	1.15	0.13
Subject 20	2.0	0.2	0.41
Subject 21	1.9	0.3	0.37

The values are given as means with standard deviations in parentheses. MMSE = Mini-Mental State Examination; IFS = INECO Frontal Screening. Table 1b provides the multiple single-case comparisons within the bvFTD group. IMJ = Impaired moral judgment; PMJ = relatively preserved moral judgment.

In addition, we estimated overall moral judgment impairment by calculating a global moral score. This score was represented by the average of the difference between raw scores for accidental and attempted harm and the maximum expected rating for each condition (7 and 1, respectively). Thus, we subtracted the accidental

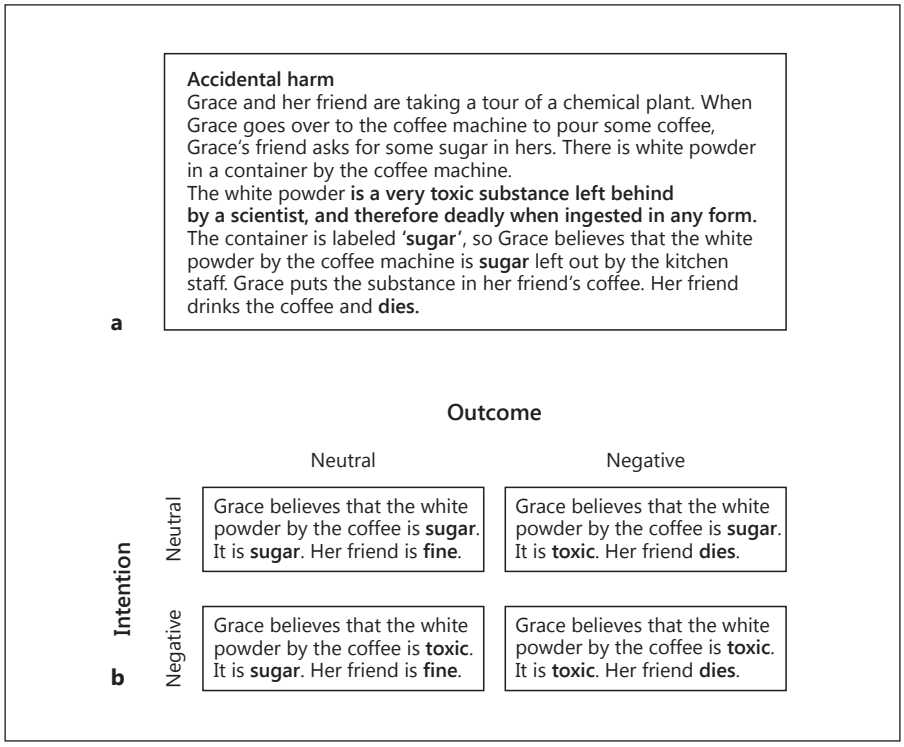


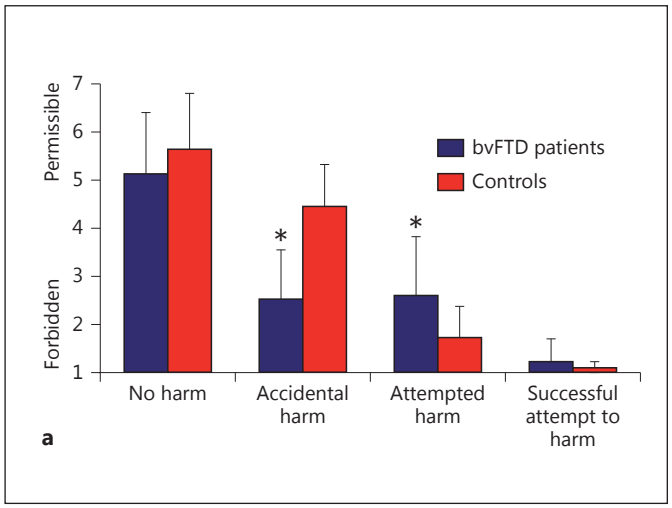
Fig. 1. Experimental design and stimuli. **a** Illustrative text of an 'accidental harm' scenario. Bold sections indicate words that differed across conditions. **b** Combination of intention (neutral vs. negative) and outcome (neutral vs. negative) factors yielding a 2 × 2 design with 4 conditions. For more examples, see the full set of scenarios in the supplementary material.

harm score from 7 and the attempted harm score from 1, and then we averaged both results. In short, the higher this global moral judgment score, the worse the sample's performance. As done in previous bvTFD studies [30, 32, 36, 37], patients were separated into two subgroups [impaired moral judgment (IMJ) and relatively preserved moral judgment (PMJ)], depending on their performance on the moral judgment task. The patients whose global score was significantly impaired compared to the control group (IMJ) were separated from the patients whose global score did not differ from that of the control group (PMJ). We obtained these classifications via multiple single-case analyses using a modified one-tailed t test for single case-group comparisons [38]. This methodology allows comparisons between the scores of each bvFTD patient and those of the control group [38, 39]. This modified test is more robust for nonnormal distributions, generates few type I errors [40], and has been employed in recent single-case studies [41–43]. Additionally, several reports [41, 44–47] have relied on this method to compare a number of measures and experimental variables of single cases with a control sample, which shows that it is a widely used strategy in the current neuropsychological literature.

We additionally employed multiple single-case analyses to compare the performance of each bvFTD patient to that of the control group in the conditions yielding significant between-group differences (accidental and attempted harms). Results of these comparisons are shown in supplementary data (online suppl. tables 1 and 2). Finally, as a complementary analysis, we calculated the difference between raw scores for accidental harm and successful attempts to harm. We subtracted the successful attempt to harm score from the accidental harm score, given that these two conditions have the same outcome but a different intention. Finally, to explore the relationship between moral judgment and executive functions, we performed correlation analyses between the global moral judgment score and the INECO Frontal Screening subtests.

VBM Analysis

Images were preprocessed using the DARTEL Toolbox according to previously described procedures [48]. Then, modulated 12-mm full-width half-maximum kernel-smoothed [49] images were normalized to the MNI space and analyzed using general linear models for second-level analyses using SPM-8 software. To identify the areas of GM atrophy in the bvFTD patients, a two-sample comparison between patients and controls was performed, including the total intracranial volume as a confounding covariate [$p < 0.05$, false discovery rate (FDR) corrected, extent threshold = 100 voxels]. For the subsequent analyses, we used a mask derived from the results of a moral cognition meta-analysis [50]. This mask included the following regions of interest: the VMPFC, the dorsomedial prefrontal cortex, the bilateral orbitofrontal cortex, the precuneus, the TPJ, the posterior cingulate cortex, the right TP, the right middle temporal gyrus and the amygdala. This mask was selected because it includes brain regions consistently reported in moral cognition studies [1, 50] and also atrophied in bvFTD [2, 24, 51]. Region of interest analysis is a standard strategy used in previous bvFTD [36, 52–55] and moral cognition [56, 57] structural neuroimaging studies. Also, this approach restricts the analysis to a small number of regions, thereby reducing the multiple comparison problems inherent in multivoxel analyses.



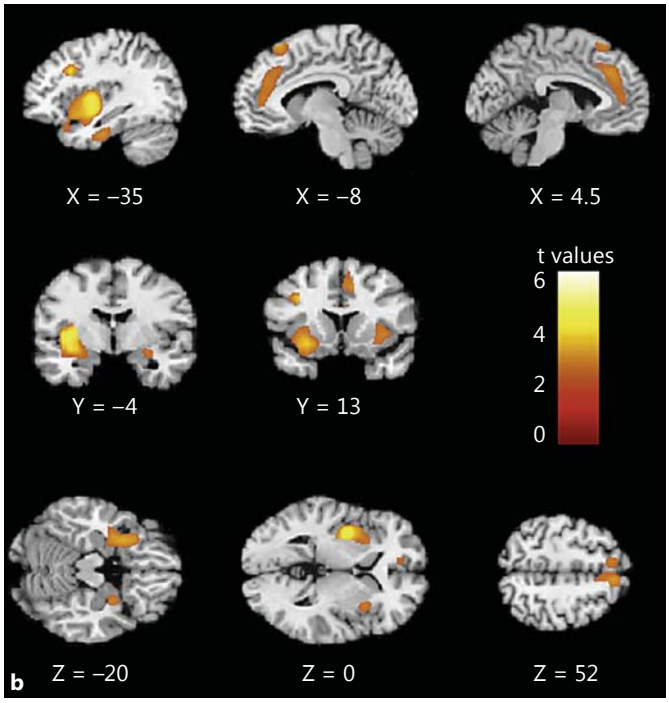


Fig. 2. Comparisons between bvFTD patients and controls. **a** Behavioral results. Moral judgments and significant differences between the groups (represented by asterisks). **b** VBM results. Regions of significant GM volume loss in the bvFTD group compared with the control group ($p < 0.05$, FDR corrected).

We used the SPM multiple regression module to determine the regions of interest in which GM volume was associated with the scores on the accidental harm, attempted harm, global moral scores, and the difference between accidental harm and successful attempted harm. Brain-behavior correlations were performed for all subjects together and then for each group independently. For all correlation analyses, we considered total intracranial volume as a covariate of no interest, and the statistical threshold was defined as $p < 0.05$ (extent threshold = 100 voxels). Finally, to identify the differences in brain atrophy between the patients exhibiting IMJ and PMJ, we compared these subgroups taking into account the previously described bvFTD classification ($p < 0.05$, FDR corrected, extent threshold = 50 voxels).

Results

Behavioral Data

Moral judgment data were normally distributed (p values >0.1). For both groups, actions with neutral intentions and neutral outcomes were judged as more permissible than actions with negative intentions and negative outcomes [main effects of intention, $F(1, 38) = 2.34$, $p < 0.001$, $\eta^2 = 0.86$, and outcome, $F(1, 38) = 111.63$, $p < 0.001$, $\eta^2 = 0.74$]. Furthermore, accidental harms were judged as more permissible than intentional harms [intention × outcome interaction, $F(1, 38) = 9.16$, $p < 0.005$, $\eta^2 = 0.19$]. There were no significant differences in nonharm [$F(1, 38) = 1.85$, $p = 0.18$, $\eta^2 = 0.04$] or successful attempt to harm judgments [$F(1, 38) = 1.64$, $p = 0.20$, $\eta^2 = 0.04$].

Significant interactions were detected between intention and group [$F(1, 38) = 23.08$, $p < 0.001$, $\eta^2 = 0.37$] and between outcome and group [$F(1, 38) = 14.68$, $p < 0.001$, $\eta^2 = 0.27$]. Planned comparisons revealed that bvFTD patients judged accidental harm as less permissible [$F(1, 38) = 39.29$, $p < 0.001$, $\eta^2 = 0.50$] and attempted harm as more permissible than controls [$F(1, 38) = 7.78$, $p < 0.005$, $\eta^2 = 0.18$]. The MMSE scores did not have significant effects on the accidental harm ($p = 0.50$) or attempted harm ($p = 0.40$) performances. There were no significant differences in nonharm [$F(1, 38) = 1.85$, $p = 0.18$, $\eta^2 = 0.04$] or successful attempt to harm judgments [$F(1, 38) = 1.64$, $p = 0.20$, $\eta^2 = 0.04$; fig. 2a].

Intragroup comparisons revealed that controls judged accidental harm as more permissible than attempted harm [$t(18) = 10.76$, $p < 0.001$]. For bvFTD patients, this difference was not detected [$t(20) = 0.22$, $p = 0.82$]. In addition, we conducted multiple single-case analyses to compare the performance of each bvFTD patient to that of the control group in the conditions yielding significant between-group differences (accidental and attempted harms). Relative to controls, 70% of the patients exhibited lower accidental harm, while the remaining 33% showed higher attempted harm scores (see online suppl. tables 1 and 2).

Table 2. Regions of significant atrophy (local maxima) in bvFTD patients compared with controls

Region	x	y	z	Cluster size	Peak t	Peak z
Mid-cingulate gyrus R	4.5	36	33	5,476	3.54	3.89
Insula L	–36	–4.5	1.4	5,009	3.97	4.47
Amygdala R	30	–2.8	–16.5	905	2.85	3.04
Inferior temporal gyrus L	–39	–16.5	–31.5	759	3.04	3.26
Middle frontal gyrus L	–34.5	15	30	290	3.45	3.77

L = Left; R = right; $p < 0.05$, FDR corrected.

Given that statistical significance depends, among other factors, on the variability of each group, we reanalyzed the data excluding subjects who were below (–2 SD) or above (+2 SD) the group's mean. The results showed the same group differences with similar effect sizes (see details in the online suppl. material).

Considering that accidental harm and successful attempts to harm have the same outcome but a different intention, we subtracted the score in the latter from that of the former condition. Compared to controls, bvFTD patients exhibited a significantly lower difference between these two conditions [$F(1, 38) = 39.88$, $p < 0.001$, $\eta^2 = 0.51$].

Regarding the relationship between moral judgment and executive functions, results from bvFTD patients showed no significant correlations between the moral global score and any of the INECO Frontal Screening subtests. In controls, the global moral score was positively correlated with the verbal inhibitory control subscale ($r = 0.54$, $p = 0.02$).

VBM Results

Global Atrophy of bvFTD Patients Compared to Controls

Compared to controls, bvFTD patients presented an atrophy pattern consistent with that reported in previous studies [24–27]. Results showed atrophy involving the medial frontal regions, the insula, the amygdala, the cingulate gyrus, and the inferior temporal gyrus (FDR corrected, $p < 0.05$; table 2, fig. 2b).

Structural Correlates of Moral Judgment

Table 3 summarizes the coordinates of peak voxels in significant clusters associating moral scores with GM volumes.

Global Score. In both groups, the global score was negatively correlated with the GM volume in the precuneus and left TPJ. In bvFTD patients, this score was associated with the GM volume in the left precuneus and TPJ, whereas in controls, it was associated with the bilateral precuneus and left TPJ (fig. 3a).

Accidental Harm. In both groups, the accidental harm score was positively correlated with the GM volume in the right precuneus and left TPJ. In patients, this score was correlated with the GM volume in the right precuneus. In controls, it was correlated with the right precuneus, the VMPFC and the dorsomedial prefrontal cortex (fig. 3b).

Attempted Harm. In both groups, the attempted harm score was negatively correlated with the GM volume in the bilateral TPJ. In bvFTD patients, this score was correlated with the bilateral TPJ, whereas in controls, it was only correlated with the left TPJ (fig. 3c).

Difference between Accidental Harm and Successful Attempt to Harm. In both groups, this score was negatively correlated with the GM volume in the right precuneus and the left TPJ. In bvFTD patients, the score was associated with the GM volume in the right superior temporal pole, whereas in controls it was associated with the left precuneus, the VMPFC, and the dorsomedial prefrontal cortex.

Structural Differences between the bvFTD Subgroups

We performed single-case analyses to compare the score of each bvFTD patient to the scores of the control group. Patients were separated into 2 groups according to their moral global score. Eleven patients were classified into the subgroup with worse performance (IMJ), and 10 were classified into the subgroup with relatively preserved performance (PMJ; table 1b). At the behavioral level, these subgroups showed no significant differences in MMSE [$F(1, 19) = 0.11$, $p = 0.73$, $\eta^2 = 0.006$] or INECO Frontal Screening [$F(1, 19) = 0.43$, $p = 0.51$, $\eta^2 = 0.02$] scores. However, as expected, the IMJ subgroup was outperformed by the PMJ subgroup in global moral score

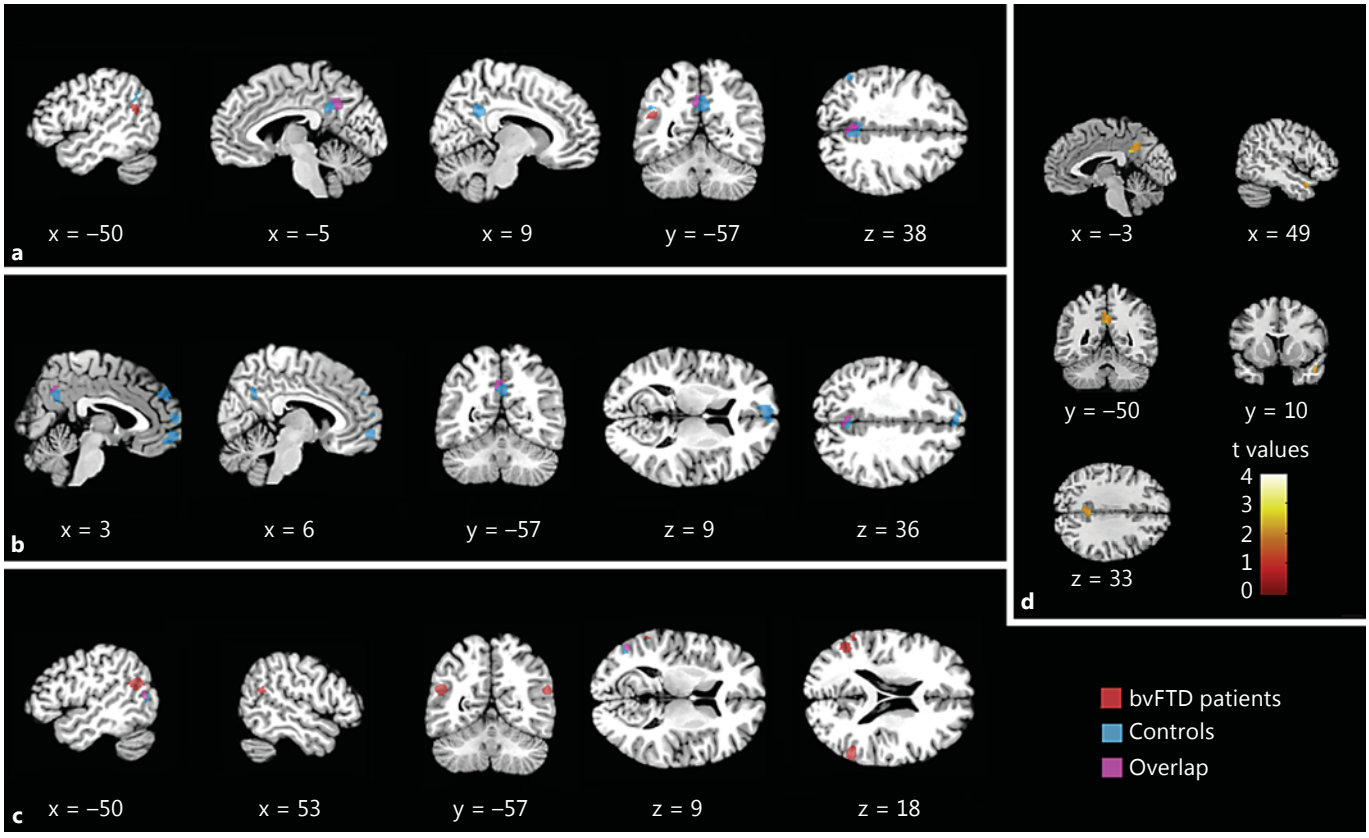


Fig. 3. Correlations and differences between the bvFTD subgroups. Regions of reduced GM density that were associated with: the moral global score (**a**), accidental harm judgment (**b**) and attempted harm judgment (**c**). **d** Regions of reduced GM density in bvFTD patients exhibiting worse performance (IMJ vs. PMJ patients) on the moral judgment task ($p < 0.05$, FDR corrected).

Table 3. Anatomic locus of peak voxels in clusters associating moral global scores to GM volumes

Region	bvFTD patients						Region	Controls					
	x	y	z	cluster size	peak t	peak z		x	y	z	cluster size	peak t	peak z
Moral global score													
Precuneus L	–6	–60	33	269	2.71	2.45	Precuneus R	3	–64	31	1,202	3.95	3.28
TPJ L	–48	–55	18	156	2.38	2.19	TPJ L	–51	–60	40	136	2.58	2.34
Accidental harm													
Precuneus R	3	–61	40	171	2.45	2.25	Dorsomedial prefrontal cortex L	–3	49	37	986	3.50	2.99
							Precuneus L	1	–61	28	436	2.87	2.55
							VMPFC R	6	54	–10	221	2.46	2.24
Attempted harm													
TPJ L	–58	–52	13	125	4.56	3.67	Middle occipital gyrus L	–49	–67	6	156	3.36	2.90
Middle occipital gyrus L	–52	–57	15	387	3.82	3.22							
TPJ R	54	–52	18	264	2.16	2.01							
Accidental harm minus successful attempt to harm													
Superior temporal pole R	49	9	–22	275	3.01	2.67	Dorsomedial prefrontal cortex L	–1	48	37	597	3.11	2.73
							Precuneus R	3	–61	28	360	2.73	2.45
							Ventromedial-orbitofrontal cortex	4	52	–12	143	2.40	2.20

L = Left; R = right; $p < 0.05$.

[$F(1, 38) = 37.70$, $p < 0.001$, $\eta^2 = 0.66$]. With regard to the structural differences, compared to the IMJ subgroup, the PMJ subgroup exhibited less atrophy in the left precuneus and the right TP ($p < 0.05$, FDR corrected, fig. 2d; $p < 0.05$, FDR corrected, fig. 3d).

Discussion

The VMPFC is known as a crucial brain area for the acquisition and maturation of moral competency [58]. The VMPFC is also recruited for the processing of emotionally charged moral stimuli [6], belief valence [59] and moral violations [5]. Despite the clear importance of the VMPFC, two primary findings of this study suggest that the neural mechanisms underlying the processing of intentions and outcomes for moral judgment are not restricted to this region. First, overall moral judgments in both groups were primarily associated with regions involved in processing intentions, such as the TPJ and the precuneus. Second, atrophy of the precuneus and the TP (a crucial region for processing social stimuli) distinguished between bvFTD patients exhibiting low and relatively spared performance. Thus, our findings indicate that processing intentions and outcomes for moral judgments relies on regions beyond the VMPFC.

Moral Judgments

This study replicated the results of a recent report [23] showing that bvFTD patients judged attempted harm as more permissible and accidental harm as less permissible than control subjects. Unlike controls, and consistently with the VBM results (see below), bvFTD patients judged attempted harm by focusing on the neutral outcome rather than the protagonist's negative intention. Similarly, bvFTD patients judged accidental harm by focusing on the negative outcome without considering the neutral intention and, as a consequence, they were less willing than controls to exonerate a protagonist for accidentally causing harm. We also calculated the difference between the scores for accidental harm and successful attempts to harm, since these two conditions have the same outcomes but different intentions. Compared to controls, bvFTD patients showed a lower difference between the scores in these conditions, which suggests that they were not able to integrate intentions and outcomes as well as control subjects did. Thus, taken together, our findings suggest that the performance of patients is characterized by an overreliance on outcome, either neutral or negative, rather than by the integration of intentions and outcomes.

In addition, to compare the performance of each bvFTD patient to that of the control group in accidental and attempted harms, we conducted multiple single-case analyses. Relative to controls, 70% of the patients exhibited lower accidental harm scores, while the remaining 33% showed higher attempted harm scores. Thus, although group analyses revealed significant differences between the bvFTD patients and controls, moral judgment impairments seem to be severer for accidental than attempted harms. Exculpating an agent who causes harm accidentally requires an especially robust representation of his intentions, as this information is critical to override a preponderant negative response to the outcome [60]. Therefore, judgments of accidental harm particularly involve the capacity to integrate the information about the agent's intention with the contextual cues of the situation, a process that seems to be impaired in bvFTD [2].

Previous studies of patients with VMPFC lesions have found similar deficits in judging attempted [21, 22] and accidental [22] harms. Furthermore, abnormalities in judging attempted harm have been reported in frontal stroke patients either with or without VMPFC involvement [23]. Together, the present and previous results suggest that the moral judgment impairments of bvFTD patients are comparable to those observed in patients with VMPFC damage.

As revealed by covariance analyses, this outcome-based moral judgment pattern observed in bvFTD patients does not seem related to general cognitive impairments. Note that the 4 task conditions involve similar cognitive and language demands; if these factors were affecting the patients' performance, difficulties should be observed across the 4 conditions and not only in those featuring accidental and attempted harm. However, further studies should assess the relationship between performance in specific cognitive domains and moral judgment in bvFTD patients. Moreover, the patients' difficulties to integrate intentions and outcomes for moral judgment may be related to impairments in theory of mind. Deficits in this ability have been reported in bvFTD patients [52, 54, 61, 63]. Given that the patients' moral judgments tended to focus on outcomes rather than intentions, their performance may have been influenced by mental-perspective-taking deficits. The association between both variables should be explored in future research on bvFTD. In addition, bodily and facial emotion recognition is affected in bvFTD patients [63, 64]. Emotion-processing deficits have been associated with moral judgment impairments [21, 65], and key brain regions involved in emotion processing (e.g. amygdala and

VMPFC) are also relevant for moral judgment [15, 66, 67]. Thus, moral judgment abnormalities in bvFTD patients may also be related to emotion-processing impairments. Further studies should explore the relationship between moral judgment and other social cognition domains in patients with bvFTD.

In addition, correlation analyses showed that in bvFTD patients, executive functions were not associated with moral judgment performance. This finding suggests that although our sample features both executive and moral judgment impairments, these two domains are independent. In line with this result, previous studies have shown that some social cognition domains, such as empathic concern of intentional harms [29], are primarily affected in bvFTD, independently from executive dysfunction. In controls, we found a significant association between the verbal inhibitory control subtest and the global moral score. However, this is an unspecific correlation that needs further exploration. No conclusive results are available in previous studies investigating the association between moral cognition and executive functions in healthy subjects and other neuropsychiatric populations. There is evidence for [68, 69] and against [70, 71] the relationship between these domains. Future studies should assess the specific relationship between moral judgment and different executive function processes using a more complete neuropsychological battery.

Structural Correlates of Moral Judgments

The global atrophy pattern of bvFTD patients involved mainly medial frontal regions, the insula, the amygdala, the cingulate gyrus, and the inferior temporal gyrus. This result aligns with the atrophy pattern previously reported in bvFTD research [24–27]. Consistently with a previous study [26] showing different atrophy patterns in bvFTD, the group of patients assessed here showed discrete orbitofrontal atrophy. This finding is still consistent with the diagnosis of bvFTD since limbic structures (e.g. cingulate and insula) also exhibit early damage in this disorder [72].

Consistent with recent studies [50, 60], the global performance of both groups was primarily associated with the GM volume in the TPJ and the precuneus. Typically, TPJ activity has been proposed to reflect inference of mental states [18]. Additionally, it integrates information from several sources (e.g. attention, memory) and helps to establish a social context for decision making [19]. All these functions are relevant processes for moral judgment. The precuneus also subserves processing of mental states [16] and integration of self-referential stimuli (e.g. a moral situation) in the broader emotional or moral context of the self [17]. Thus, our results align with previous evidence implicating the TPJ and the precuneus in moral judgment processes.

In both groups, greater willingness to exculpate protagonists who accidentally cause harm was associated with larger GM volume in the precuneus. When judging accidental harm, individuals must use intention information to override a preponderant negative response to the outcome [59]. This may partly explain the involvement of the precuneus. Moreover, under these conditions, the negative outcome contains the more salient information. Therefore, in judgments of accidental harm, information about the agent's intention must be integrated with the outcome information, a process that appears to engage the VMPFC [22]. GM volume in this region was associated with judgments of accidental harm only in controls. This pattern aligns with behavioral results showing bvFTD patients focus more on negative outcomes than on the integration of intentions and outcomes.

Regarding attempted harm, the performance of both groups was associated with the GM volume in the TPJ. This region is more active for attempted harm compared to other conditions [60]. Furthermore, transcranial magnetic stimulation of the right TPJ reduces reliance on the protagonist's intention and moral objections to attempted harm [73]. In the case of attempted harm, the outcome is neutral; therefore, the intention to harm is the most salient information. Thus, appropriate moral judgments primarily depend on considering the harmful intention of the agent, a process in which the TPJ appears to play a crucial role.

Consistently, the difference between accidental harm and successful attempt to harm was associated in both groups with GM volumes in the TPJ and the precuneus. In bvFTD patients, this difference was associated with GM volume in the right superior temporal pole. The TP supports processing of personally relevant social information [74], leads to social cognition impairments when affected by neurodegeneration [75], and is recruited during moral decision making [6]. In controls, the difference was related with GM volumes in the precuneus and the VMPFC, which is consistent with the involvement of both regions in processing intentions [16] and integrating the agent's intention with the outcome information [22].

In addition, bvFTD patients were divided into two groups according to their moral global score. Eleven patients were classified into the subgroup with worse performance, and 10 were classified into the subgroup with relatively preserved performance. Such between-patient variability aligns with the clinical heterogeneity of bvFTD [76,

77] and is consistent with previous studies [33, 78] showing that a proportion of bvFTD patients do not exhibit moral judgment impairments. A two-sample comparison showed that patients exhibiting greater moral judgment impairments displayed smaller GM volumes in the precuneus and the right TP. These findings are coherent with the regression analyses and consistent with previous studies [1, 50, 69], suggesting that these brain regions are fundamental for judging accidental and attempted harms.

Implications and Future Directions

Although the patients who participated in this study fulfilled criteria for probable bvFTD, as in many other reports [27, 28, 30–33, 61, 62, 78, 79], a biomarker against Alzheimer's disease is not available, which constitutes a limitation of our work. Future studies should further explore structural correlates of moral judgment in bvFTD patients with biomarker measurements as well as in other variants of frontotemporal dementia.

Our results indicate that moral judgment impairments in bvFTD are not exclusively associated with VMPFC damage. Rather, such deficits are related to the integrity of multiple structures, including the TPJ, the precuneus, and the TP. In line with our findings, a recent study [80] used conjunction analysis to explore whether regions consistently affected in bvFTD converge with those implicated in moral judgment. Results showed that the anterior frontomedian and paracingulate cortices are atrophied regions particularly relevant for moral cognition impairments in bvFTD. Further empirical studies should assess how the specific atrophied regions in bvFTD affect these patients' moral judgment.

Supporting this concept, the event-feature-emotion complex model [1] proposes that moral cognition is not restricted to any particular brain region, but rather emerges from the integration of content and context-dependent representations in cortical-limbic networks. In line with this model, the social context network model [2] describes the contextual influence on social cognitive processing as dependent on a frontotemporal network. As shown in this and previous studies [24, 25], structures proposed to be important in these models are affected in bvFTD.

Notably, several regions associated with moral judgment (medial prefrontal cortex, TPJ and precuneus) are components of the default mode, the activity of which temporally correlates with moral judgment performance [81] and is involved in the moral cognition impairments of bvFTD patients [82]. These findings further support the hypothesis that moral judgment impairments in bvFTD may be explained by the disruption of extended brain networks.

In conclusion, this is the first study on bvFTD that assesses structural correlates of intention and outcome processing for moral judgment. Our findings support previous research showing that the atrophy pattern of bvFTD extends beyond the VMPFC, and include other frontal-temporal-insular brain regions [24, 25]. Furthermore, the present results suggest that the TPJ, the precuneus, and the TP are associated with moral judgment abnormalities in bvFTD. These areas seem to include critical hubs within an extended moral network supporting the processing of intentions and outcomes.

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Disclosure Statement

The authors declare no competing financial interests.

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