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Research Article

Neural correlates of empathic impairment in the behavioral variant of frontotemporal dementia

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Abstract

Objective: Loss of empathy is a symptom of the behavioral variant of frontotemporal dementia (bvFTD), constituting a clue for early diagnosis. In this study, we directly compared two empathy components (intention attribution [IA] and emotion attribution [EA]), correlating them with possible specific patterns of gray-matter density reduction within the mentalizing network.

Methods: We evaluated IA and EA in 18 mild bvFTD patients compared with 36 healthy controls (HCs) using a single nonverbal test. A subgroup entered a voxel-based morphometry study.

Results: Compared with HC, bvFTD patients showed IA and EA impairments. EA performance correlated with gray-matter reduction in the right amygdala, left insula, and posterior-superior temporal sulcus extending into the temporoparietal junction.

Conclusion: We proved an empathic impairment, with the ability to infer emotional states showing the most severe deficit. These results provide further evidence of selective disease-specific vulnerability of the limbic and frontoinsular network in bvFTD and highlight the usefulness of empathy assessment in early patients.

Keywords: Behavioral variant of frontotemporal dementia; Empathy; Mentalizing; Social cognition disorders; Voxel-based morphometry

1. Introduction

The most common clinical manifestations of the behavioral variant of frontotemporal dementia (bvFTD) are changes of personality and social conduct [1]. The recent revision of the diagnostic criteria includes an early loss of sympathy and empathy occurring within the first 3 years of illness among the diagnostic symptoms [2]. These symptoms are defined clinically as "diminished response to other people's needs and feelings; and diminished social interest, interrelatedness or personal warmth." It is noteworthy that standard neuropsychological batteries are not sensitive to the early executive and social behavior impairments, including loss of empathy, characterizing this clinical subtype [3].

Empathy in itself represents a complex and heterogeneous construct, the definition of which and functional characterization is still debated [4,5]. Empathic abilities cover several phenomena, ranging from automatic affect sharing (i.e., emotional contagion) to the attribution of mental states, including emotional states or intentions [5]. Several studies have shown that, at the neural level, representing different kinds of another's mental states engages overlapping and segregated neural systems [6,7]. On the one hand, imaging studies in normal subjects have associated a general ability in the attribution of mental states (i.e., mentalizing) with a broad network of areas including the medial prefrontal

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cortex (mPFC), temporoparietal junction (TPJ), temporal poles, and medial precuneus [8,9]. On the other hand, neurological evidence resulting from lesion and imaging studies in patients [6,7] supports the distinction between the attribution of cognitive states (associated with the mPFC [6]) versus emotional states (involving the frontoinsular cortex [6,10] and limbic regions such as the amygdala [11]).

Many of these brain regions have been reported to be damaged in bvFTD, even in the early stages [12]. In addition, the effect of the localized gray matter (GM) loss in frontal paralimbic areas on mentalizing abilities [13–23], emotional reactivity, emotion recognition [24,25], and self-awareness [22,26,27] has been widely investigated in frontotemporal dementia, although the notion that mentalizing and emotional facial recognition impairments are specific features of frontotemporal lobar degeneration (FTLD) has recently been challenged [28].

It is noteworthy that deficits in the attribution of cognitive versus emotional states have never been compared directly in the same patient group using a single task nor correlated with possible specific patterns of GM reduction within the mentalizing network.

Thus, the main purpose of this study was to investigate, within the same sample of bvFTD patients and with a single task, the putative alterations of the ability to infer others' intentions versus emotions as well as to relate performance with anatomical damage in specific neural subsystems. We predicted impaired performance in both facets of empathy, but particularly in the attribution of emotional states. Moreover, we predicted that, although deficits in intention and emotion attribution correlate with atrophy in regions associated with mentalizing abilities, only emotion attribution requires the additional engagement of limbic structures.

2. Materials and methods

2.1. Participants

Eighteen mild dementia patients (13 men, 5 women; mean age = 63.36 years; standard deviation [SD] = 7.47; Clinical Dementia Rating scale [CDR] global score $\leq$1) fulfilling clinical criteria for probable bvFTD [2,29,30] and 36 healthy controls (HCs; 26 men, 10 women; mean age = 62.83 years; SD = 7.95; range 43–79) were included in the study (see Table 1).

All patients were consecutively recruited from the Department of Clinical Neurosciences, Vita-Salute University and San Raffaele Scientific Institute (Milan, Italy) and evaluated by a team of experienced behavioral neurologists and neuropsychologists. Patients and caregivers underwent a structured clinical interview. In addition to the main experimental task (see below), all subjects also underwent a full neurological examination, a standard neuropsychological battery including measures of executive functions (i.e., Digit Span, Raven's Progressive Matrices, Attentive Matrices), and a neurobehavioral assessment (i.e., Neuropsychiatric Inventory and Frontal Behavioral Inventory). Instrumental data including neurophysiological (i.e., electroencephalogram [EEG]) and neuroimaging (i.e., brain magnetic resonance imaging [MRI] or computed tomography [CT], cerebral fludeoxyglucose-positron emission tomography [[^{18}F]FDG-PET] or SPECT) data were also collected for each patient. The exclusion criteria were a Mini-Mental State Examination (MMSE) raw score below 21/30 and a CDR global score above 1.

Table 1
Demographic and clinical features of the sample

	bvFTD (n = 18)	HC (n = 36)	t statistics	P
Age in years	63.36 (7.47)	62.83 (7.95)	0.24	.81
Education in years	11.33 (3.6)	10.03 (3.65)	1.24	.22
Disease duration in months	6.67 (15.56)	-	-	-
MMSE	25.83 (3.27)	28.75 (0.84)	−5.06	<.0001
FBI	23.62 (7.87)	-	-	-
NPI	30.37 (16.39)	-	-	-
CDR sum of boxes	3.97 (2.52)	-	-	-
FTLD-CDR sum of boxes	5.65 (2.97)	-	-	-

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; HC, healthy control; MMSE, Mini-Mental State Examination; FBI, Frontal Behavioral Inventory; NPI, Neuropsychiatric Inventory; CDR, Clinical Dementia Rating scale; FTLD-CDR, FTLD-modified CDR.

NOTE. For each variable, the mean and standard deviation, as well as the t statistics and P value of between-group comparisons, are shown.

HCs were recruited at local senior community centers. Their inclusion criteria were the absence of any neuropsychiatric disorder, a normal neurologic examination, a CDR of 0, a MMSE raw score of 28/30 or greater, and verbal and visuospatial delayed memory performance of the 25th percentile or greater. None was taking medications interfering with neurobehavioral functioning. A close informant (e.g., spouse) of each control subject was interviewed to corroborate the normal daily functioning of the subject. There was no significant difference between bvFTD and HC in gender, age (two sample t test; $t(52) = 0.24$, $P > .05$), or educational level ($t(52) = 1.24$, $P > .05$).

All subjects, or their informants/caregivers, gave informed consent to the experimental procedure that had been approved by the local ethical committee.

2.2. Experimental assessment

All subjects were administered a nonverbal task assessing the attribution of mental states to other individuals, specifically requiring the recognition of their intentions versus emotional states, as well as the ability to infer physical causal relationships devoid of social components. The task procedure and stimuli were developed ad hoc for this study and derive from those previously used by Sarfati and colleagues [31], Brunet and colleagues [32], and Völlm and colleagues [33]. Some stories were modified in their content and others were added de novo. A professional graphic designer drew all strips (see an example in Figure 1). We used a nonverbal task to avoid

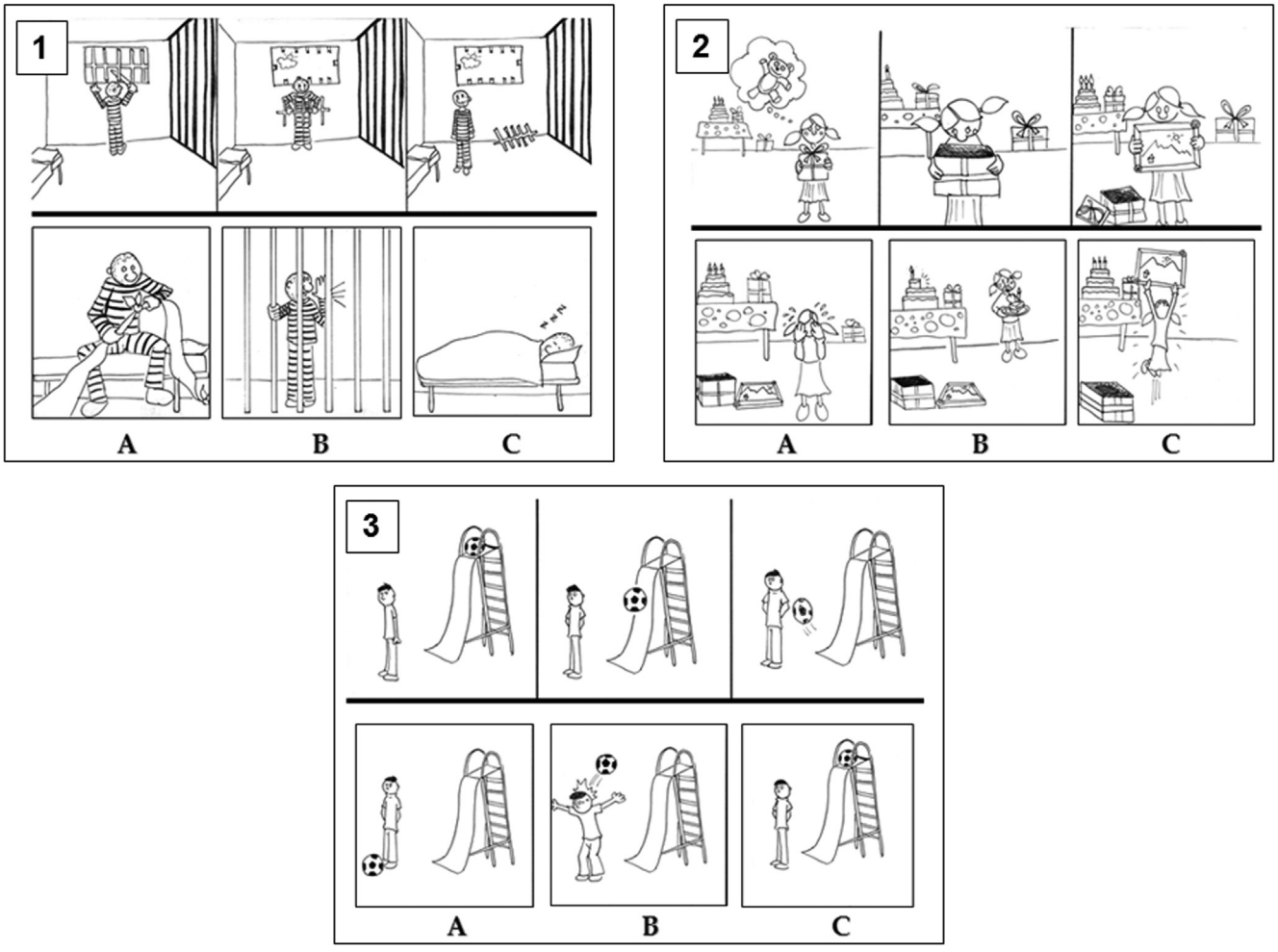

Fig. 1. Example of a comic strip from the (1) intention attribution; (2) emotion attribution, based on sadness; and (3) causal inference conditions. The three pictures at the top depict the story whereas those at the bottom show its possible endings (A, B, or C).

possible confounds deriving from linguistic abilities. Because bvFTD patients may present language disorders related to the extension of the degenerative process to linguistic networks, a nonverbal task offers the opportunity to evaluate the empathic abilities in a wider sample of bvFTD patients.

The whole task consists of two main experimental conditions (i.e., identifying intentions [intention attribution {IA}] and emotional states [emotion attribution {EA}]) plus a control condition entailing the comprehension of causality reaction on the basis of knowledge about the physical properties of object or human bodies (causal inferences [CI]). The task includes six trials per condition randomly presented following the procedure of Völlm and colleagues [33]. The subjects' task is to select the correct ending of a comic strip among three different options (plausible, implausible, and plausible but incorrect, in random position across different trials). Unlike Völlm and colleagues [33], we used the same general question across experimental conditions (i.e., "What is the correct ending of the story?") to prevent the induction of specific strategies that may confound the interpretation of specific story-content effects.

Stimuli had been selected in a preliminary pilot study in two groups of 20 healthy young subjects each. Subjects from the first group (10 men, 10 women; mean age = 28.33 years, SD = 5.42) were administered the same experimental procedure as that described above. In contrast, subjects from the second group (10 men, 10 women; mean age = 27.89 years, SD = 3.22) underwent the procedure used by Völlm and colleagues [33]. A 5-point Likert-type rating scale was used, with 5 indicating maximal clarity. Average rating scores of the finally included stories were 4.44 (SD = 0.45) for overall clarity, 4.38 (SD = 0.47) for intention attribution in the IA task, and 4.5 (SD = 0.3) for emotional states attribution in the EA task with no significant difference across conditions. In addition, participants provided sensible descriptions of the storyline and used mentalistic and emotional terms to describe the intentions and emotions of the main character. Overall, the results of the pilot assessment indicated that the included cartoons were easy to comprehend and that they elicited the understanding of intentions and emotional states of the main character of the story.

2.3. Neuroimaging data

2.3.1. MRI data acquisition

A subset of 14 bvFTD and 20 gender- and age-matched HCs underwent a magnetic resonance scanning session including T1-weighted images (220 slices, TR = 600 ms, TE = 20 ms, in-plane resolution 0.9 × 0.9 × 0.8 mm^3) collected with a 3-T Philips Achieva scanner (Philips Medical Systems, Best, NL) using an eight-channel Sense head coil. The other four bvFTD patients dropped out from this part of the study because of the presence of a pacemaker, claustrophobia, or refusal.

2.3.2. Voxel-based morphometry data preprocessing, and statistical analysis

Voxel-based morphometry (VBM) preprocessing and statistical analyses were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de) on Matlab v7.4 (Mathworks, Inc., Sherborn, MA). VBM entailed four main steps: (1) spatial normalization of all images to a standardized anatomical space using the iterative high-dimensional normalization approach provided by the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL toolbox), (2) extraction of GM and white matter (WM) from the normalized images, (3) smoothing (8 mm) of the normalized images, and (4) statistical analysis of local differences in GM density values across the whole brain.

2.3.3. Whole-brain and correlation analyses

In whole-brain analyses, regional GM density differences between bvFTD patients and healthy subjects were investigated using a two-sample *t* test on the images resulting from VBM preprocessing with education as a nuisance variable. Correlation analyses were then performed between GM density and experimental task scores, separately for IA, EA, and CI conditions, in the bvFTD sample. The statistical threshold was set at $P < .05$ family-wise error (FWE) corrected for multiple comparisons at the cluster-level. To test the actual impairment of the regions showing a correlation with performance in bvFTD patients, for all bvFTD and HC subjects we extracted the mean GM density from the clusters resulting from correlation analyses. These values were then entered into offline statistical analyses to directly compare GM density across bvFTD and HCs.

Cerebral regions showing significant effects were identified using the SPM-Anatomy toolbox v1.8 [34].

3. Results

3.1. Behavioral results

We first assessed the effects of group and subconditions on global performance (Mann-Whitney U) as well as the correlations between global task performance and other neuropsychological measures (Spearman rank order correlations). Mean global score was significantly lower in bvFTD patients (mean = 10.11, SD = 4.44) than in HCs (mean = 14.83, SD = 2.85) (U = 129, $P < .0005$) with highly variable performance among patients. The performance at single experimental conditions was also significantly worse in bvFTD patients compared with HCs. Compared with HCs, bvFTD patients displayed significantly lower mean scores in IA and EA conditions ($P < .0001$), but not in the control condition CI (U = 235.5, $P > .05$) (see Figure 2).

Within-group effects of all conditions were assessed using a Wilcoxon signed ranks test. A significant effect of the task specifically emerged in bvFTD patients, who showed a significantly lower score in the EA condition compared with the IA (Z = 2.07, $P < .05$) and CI (Z = 2.82, $P < .005$) conditions. No such effect emerged in HCs in any condition.

Correlation analyses did not show a significant relationship between task conditions and MMSE scores (IA: $r = 0.36$, $P = .14$; CI: $r = -0.02$, $P = .94$; EA: $r = 0.40$, $P = .10$). In addition, only the scores in the CI condition were significantly correlated with measures of executive functioning (Digit Span: $r = 0.83$, $P < .005$; Raven's Progressive Matrices: $r = 0.80$, $P < .01$; Attentive Matrices: $r = 0.86$, $P < .005$). No significant correlation was observed between story-based empathy task (SET) performance and other neuropsychological test scores or severity and duration measures.

3.2. VBM analysis

As expected, whole-brain analyses on GM density revealed, in bvFTD patients compared with HCs, a specific

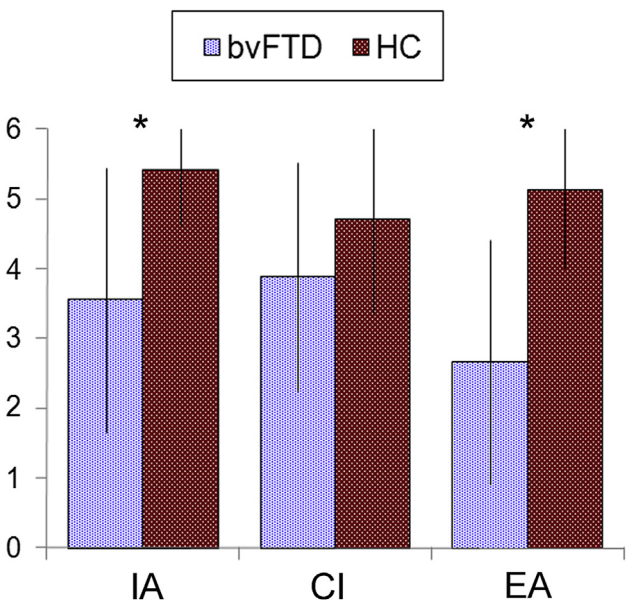

Fig. 2. The performance on the IA, EA, and CI experimental conditions is depicted separately for bvFTD patients (light blue columns) and HCs (red columns). Each condition has a maximum subscore of 6. Asterisks depict significant *P* values ($P < .0001$). Vertical bars represent standard deviations. Abbreviations: IA, intention attribution; EA, emotion attribution; CI, causal inference; bvFTD, behavioral variant of frontotemporal dementia; HCs, healthy controls.

atrophic pattern involving paralimbic (anterior cingulate, extending from dorsal to subgenual portions) and limbic (amygdala) regions, subcortical areas, and the medial anterior temporal and prefrontal cortex (see Figure 3).

Whole-brain correlation analyses between neural structure and behavioral performance showed, in bvFTD patients, a significant relationship between the score of the EA condition and GM density in four clusters, specifically involving the right amygdala along with parahippocampal gyrus and temporal pole, the left posterior insula extending into the secondary somatosensory cortex SII, the left posterior superior temporal sulcus (pSTS) extending into the TPJ, and the medial precuneus (extending ventrally to the lingual gyrus and dorsally to the posterior cingulate cortex) (see Figure 4 for details). The latter region was the only one in which GM density was also significantly correlated with performance in the IA task. This common effect was confirmed by a conjunction-null analysis [35] across the two statistical maps. However, offline analyses on mean GM density in the observed clusters confirmed that, among the regions showing a significant correlation with EA, GM density was also significantly reduced in bvFTD compared with HC only in the right amygdala, left insula, and left pSTS. No such significant group effect was observed in the medial precuneus, where GM density was significantly related with EA and IA. Finally, no significant correlation was observed in the CI control condition.

4. Discussion

Changes in social behavior are commonly reported by bvFTD caregivers since the very beginning of the disease. Nevertheless, these alterations may be difficult to recognize and quantify on the basis of a purely clinical assessment. This difficulty may contribute to the diagnostic delay, especially in subjects having no close family members or caregivers able to record these putative personality changes. The diagnosis of bvFTD is often based on clinical impressions and standard neuropsychological tests frequently lacking sensitivity to those social and emotional disturbances that characterize the disease since an early phase [36]. Thus, simple tools aimed at quantifying those behavior and personality changes reported by caregivers are useful additions to the standard neuropsychological battery for bvFTD. Ideal candidates are represented by tasks specifically evaluating those facets of social cognition that appear to be impaired since the early phases of the disease, such as empathy.

Different studies have already reported, in bvFTD patients, defective performance in tests assessing the ability to infer either intentions [13,15,16,18,23,28] or emotional states [17,19]. Here, we have assessed for the first time both components within a single task. Moreover, we have explored the neural correlates of task performance for each component in a homogeneous sample of patients, thereby reducing the possible confounds due to task and sample differences.

The significant impairment of both facets of empathy in mild bvFTD patients, compared with HCs, confirmed the importance of a thorough assessment of empathic abilities since the early disease phase. It must be underlined that SET performance was highly variable among bvFTD patients and that it was not related with any neuropsychological measure. It is important to note that no significant correlation was observed between experimental conditions and clinical severity or disease duration, suggesting the existence of phenotypic variation in the profile of task performances among patients. Further studies with larger patient samples are needed to target syndromic groups of bvFTD patients related to social cognition ability.

As expected, we found no correlation between executive measures and experimental conditions. Thus, these results suggest a relative specificity of empathic processing in the social domain from executive functioning, which, in contrast, is required by processing abstract relationships

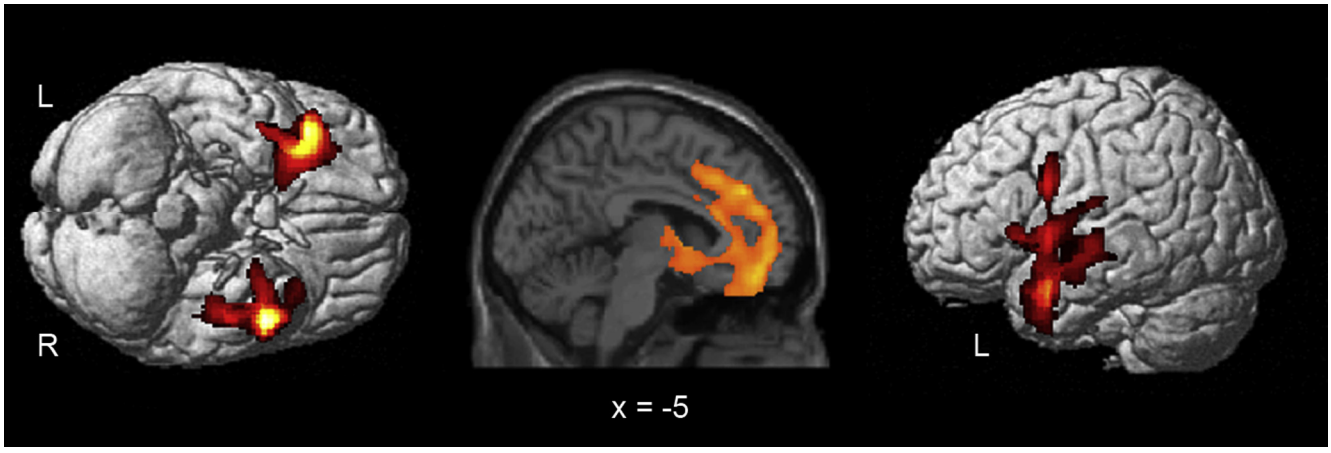

Fig. 3. The pattern of regional GM density reduction in bvFTD patients compared with HCs is depicted on three-dimensional renders and a sagittal slice ($x = -5$) of a standard template brain. Abbreviations: GM, gray matter; bvFTD, behavioral variant of frontotemporal dementia; HCs, healthy controls; L, left; R, right.

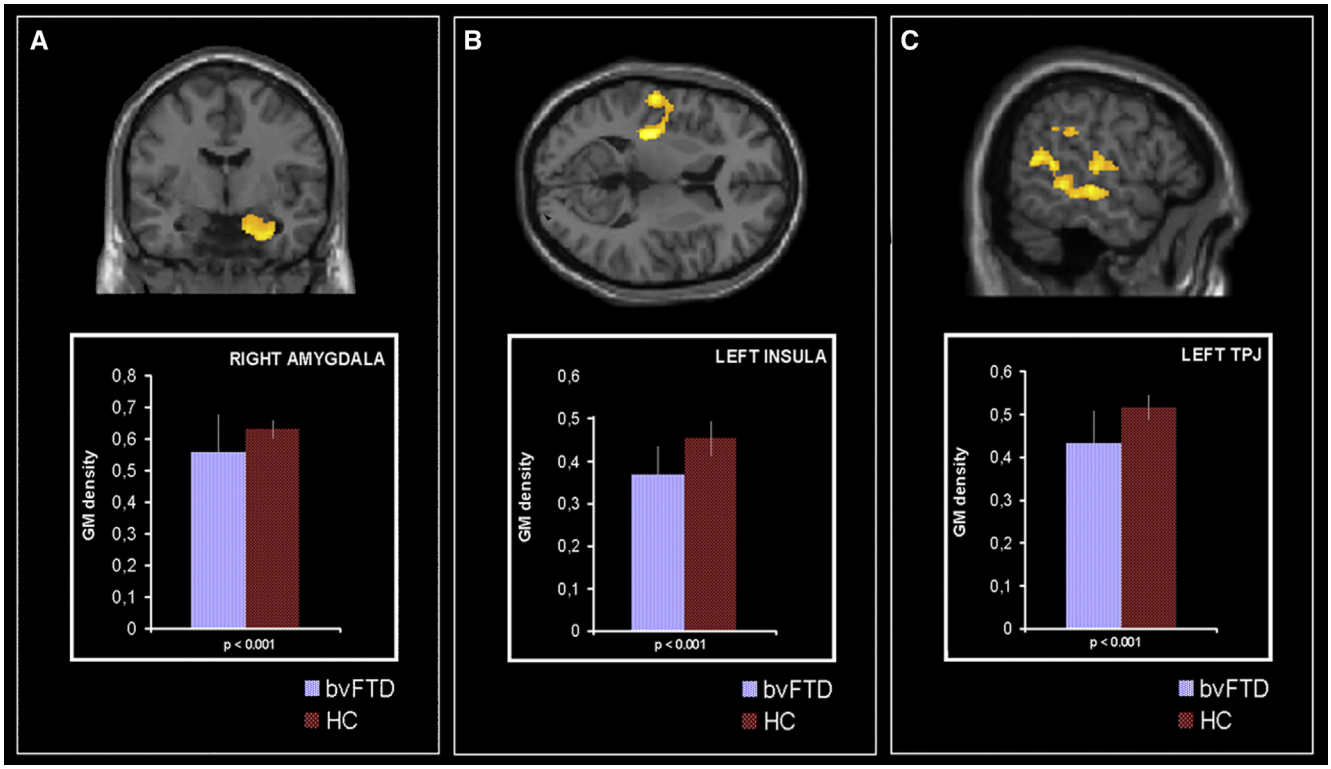

Fig. 4. Correlation analysis between GM density and EA in patients, highlighting (A) the right amygdala and hippocampus, (B) the left posterior insula, and (C) the left posterior superior temporal sulcus extending into the TPJ. Histograms show average GM density in the cluster. Vertical bars represent standard deviations. Abbreviations: GM, gray matter; EA, emotion attribution; TPJ, temporoparietal junction.

devoid of social components. In addition, the recognition and attribution of emotional states were particularly impaired in mild bvFTD patients, even when directly compared with the attribution of intentions. In line with previous reports of selective fronto-temporal-limbic damage in early bvFTD [17,19], an impairment of empathic abilities may thus represent a possible clinical-neuropsychological early marker of the disease. Therefore, an in-depth neuropsychological evaluation, specifically including the assessment of social cognition abilities, may thus prove useful to detect mild and subclinical dysfunctions in bvFTD in a very early stage. The inclusion of short and easy-to-administer social cognition tasks, as the one used here, could indeed provide objective proof of "empathy and sympathy impairments," which are one of the main criteria for the current classification of bvFTD [2]. Moreover, the use of a single test assessing different facets of empathy may reduce the inconsistencies across studies and improve the definition of the clinical phenotype. It is surprising that, despite our test results, only a few caregivers spontaneously complained of the presence of empathy and/or sympathy deficits during the clinical interview.

Recent neuropathological findings indicate a selective disease-specific vulnerability of the limbic and fronto-insular network in bvFTD [37], which is specifically involved in empathy [6]. In line with these findings, here we showed that performance in the EA condition was specifically related to GM density in the posterior insula and amygdala along with the parahippocampal gyrus and temporal pole. It is not surprising that the affective nature of the states to be represented in this condition engages the amygdala and posterior insula (extending into secondary somatosensory cortex SII). Both of these regions are known to be involved in "empathetic" brain responses to others' emotional experiences in healthy individuals [16].

A relationship between the attribution of affective states (EA condition) and GM density in the amygdala and temporal pole is consistent with recent proposals concerning the relevant role of the latter structure in high-level "conceptual" representations of the emotional valence of stimuli, including those eliciting an empathic resonance, as well as in the modulation of visceral emotional functions in response to emotionally evocative perceptual stimuli [38]. Thus, this structure may link high-level sensory representations with emotional responses, exerting a crucial role in complex emotional tasks, particularly those involving the social sphere. Furthermore, we showed a relationship between EA condition and GM density in the lateral temporal cortex, a key region in the first stages of social perception, with the pSTS acting as a multimodal hub for information concerning biological motion [39] and likely representing the input to the frontoparietal mirror system [40].

EA performance also correlated with GM density in the TPJ, which is considered a low-level mentalizing region

involved in representing others' mental states while concurrently keeping one's own perspective [11,41,42]. It is important to note that we did not find any correlation between performance on the IA task and GM density in the pSTS or TPJ, previously associated with mentalizing [9]. However, our small sample size does not allow one to conclude that this effect can be considered as specific for emotional empathy.

VBM correlation analyses also showed that performance on EA and IA conditions was related to GM density in a caudal occipitoparietal cluster, extending from the lingual gyrus to the medial precuneus and posterior cingulate cortex. The same region was found to be activated by Völlm and colleagues [33] during an identical task, as well as in a recent meta-analysis of neuroimaging studies on mentalizing [43]. Because of its strong connections with medial (posterior cingulate cortex) and lateral (angular gyrus) network components, this region, integrating memory, motor, and somatosensory inputs, may play a crucial role in the generation of mental imagery [44]. In turn, the latter would represent a basic prerequisite to infer others' mental states, regardless of their emotional versus cognitive nature [45]. However, it is important to note that in this posterior cluster we observed only a marginal and nonsignificant reduction of GM density in bvFTD patients compared with HCs. This finding may be compatible with the milder impairment of cognitive versus emotional state attribution observed in our patients.

The main limitations of this study are represented by sample size and the lack of neuropathological validation for bvFTD cases. For this reason, the results presented here should be considered preliminary. Nevertheless, the use of strict inclusion criteria [2] resulted in a well-defined experimental sample, providing further clues into the specific features of empathic impairments and the underlying neural substrates in bvFTD [2]. Given the neuropathological evidence of early vulnerability of the frontoinsular network in bvFTD [37], specific quantitative tools assessing social cognition disorders, and particularly an empathic impairment, are necessary for a rapid, yet thorough, and objective evaluation of these disorders in bvFTD patients to improve diagnostic accuracy, particularly in atypical cases.

Further work is needed to unveil the precise relationship between specific social cognition deficits and specific neurostructural impairments as well as to improve the definition of the symptoms associated with early pathological changes. Combined studies evaluating GM and WM disruption, as well as using direct measures of affective response (e.g., skin conductance response), may prove extremely useful in this regard. Moreover, investigating specific FTLD subtypes, as well as correlations with further tasks or caregiver questionnaires for empathic ability (e.g., Interpersonal Reactivity Index [17]), could highlight more subtle deficits than those currently reported. In addition to its theoretical interest, the identification of empathy impairments may entail practical implications for the management of patients and should be appropriately taken into account in the evaluation of novel symptomatic therapeutic approaches (e.g., oxytocin administration [45]).

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: This was a literature review about social cognition disorders, in particular empathy, in bvFTD that was based on a Medline and Psychlit search.
2. Interpretation: We used for the first time within the same sample of bvFTD patients a single task to assess IA and EA within the same overall design and type of stimuli, and we correlated behavioral performance with GM density. We found empathy impairment and provided evidence of the selective disease-specific vulnerability of the frontoinsular network in bvFTD.
3. Future directions: Future directions include extending this approach using multiple, theory-driven measures; increasing the specificity and sensitivity of quantitative assessments of social cognition disorders, in particular empathy, for early diagnosis in bvFTD; addressing not only regional GM but also WM disruption and measures of functional integration (structural and functional connectivity); and using direct measures of affective response (e.g., psychogalvanic reflex).

References

[1] Seelaar H, Rohrer JD, Pijnenburg YA, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry 2011;82:476–86.

[2] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134(pt 9):2456–77.

[3] Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F. A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. Brain 2009; 132(pt 5):1299–309.

[4] Preston SD, de Waal FB. Empathy: its ultimate and proximate bases. Behav Brain Sci 2002;25:1–20. discussion 20–71.

[5] de Vignemont F, Singer T. The empathic brain: how, when and why? Trends Cogn Sci 2006;10:435–41.

[6] Shamay-Tsoory SG, Aharon-Peretz J, Perry D. Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. Brain 2009;132(pt 3):617–27.

[7] Gallese V. The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. Psychopathology 2003;36:171–80.

[8] Frith U, Frith CD. Development and neurophysiology of mentalizing. Phil Trans Royal Soc B Biol Sci 2003;358:459–73.

[9] Van Overwalle F, Baetens K. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. Neuroimage 2009;48:564–84.

[10] Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science 2004;303:1157–62.

[11] Decety J. The neurodevelopment of empathy in humans. Develop Neurosci 2010;32:257–67.

[12] Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 2008; 65:249–55.

[13] Lough S, Kipps CM, Treise C, Watson P, Blair JR, Hodges JR. Social reasoning, emotion and empathy in frontotemporal dementia. Neuropsychologia 2006;44:950–8.

[14] Rosen HJ, Perry RJ, Murphy J, Kramer JH, Mychack P, Schuff N, et al. Emotion comprehension in the temporal variant of frontotemporal dementia. Brain 2002;125(pt 10):2286–95.

[15] Gregory C, Lough S, Stone V, Erzinclioglu S, Martin L, Baron-Cohen S, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. Brain 2002;125(pt 4):752–64.

[16] Eslinger PJ, Moore P, Anderson C, Grossman M. Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia. J Neuropsych Clin Neurosci 2011;23:74–82.

[17] Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. Brain 2006;129(pt 11):2945–56.

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

[19] Kipps CM, Nestor PJ, Acosta-Cabronero J, Arnold R, Hodges JR. Understanding social dysfunction in the behavioural variant of frontotemporal dementia: the role of emotion and sarcasm processing. Brain 2009;132(pt 3):592–603.

[20] Shany-Ur T, Poorzand P, Grossman SN, Growdon ME, Jang JY, Ketelle RS, et al. Comprehension of insincere communication in neurodegenerative disease: lies, sarcasm, and theory of mind. Cortex 2012;48:1329–41.

[21] Rosen HJ, Pace-Savitsky K, Perry RJ, Kramer JH, Miller BL, Levenson RW. Recognition of emotion in the frontal and temporal variants of frontotemporal dementia. Dement Geriatr Cogn Disord 2004;17:277–81.

[22] Sturm VE, Rosen HJ, Allison S, Miller BL, Levenson RW. Self-conscious emotion deficits in frontotemporal lobar degeneration. Brain 2006;129(pt 9):2508–16.

[23] Kosmidis MH, Aretouli E, Bozikas VP, Giannakou M, Ioannidis P. Studying social cognition in patients with schizophrenia and patients with frontotemporal dementia: theory of mind and the perception of sarcasm. Behav Neurol 2008;19:65–9.

[24] Omar R, Henley SM, Bartlett JW, Hailstone JC, Gordon E, Sauter DA, et al. The structural neuroanatomy of music emotion recognition: evidence from frontotemporal lobar degeneration. Neuroimage 2011;56:1814–21.

[25] Werner KH, Roberts NA, Rosen HJ, Dean DL, Kramer JH, Weiner MW, et al. Emotional reactivity and emotion recognition in frontotemporal lobar degeneration. Neurology 2007;69:148–55.

[26] Rankin KP, Baldwin E, Pace-Savitsky C, Kramer JH, Miller BL. Self-awareness and personality change in dementia. J Neurol Neurosurg Psychiatry 2005;76:632–9.

[27] Williamson C, Alcantar O, Rothlind J, Cahn-Weiner D, Miller BL, Rosen HJ. Standardised measurement of self-awareness deficits in FTD and AD. J Neurol Neurosurg Psychiatry 2010;81:140–5.

[28] Freedman M, Binns MA, Black SE, Murphy C, Stuss DT. Theory of mind and recognition of facial emotion in dementia: challenge to current concepts. Alzheimer Dis Assoc Disord 2013;27:56–61.

[29] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–54.

[30] McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001;58:1803–9.

[31] Sarfati Y, Hardy-Baylé MC, Besche C, Widlöcher D. Attribution of intentions to others in people with schizophrenia: a non-verbal exploration with comic strips. Schizophr Res 1997;25:199–209.

[32] Brunet E, Sarfati Y, Hardy-Baylé MC, Decety J. A PET investigation of the attribution of intentions with a nonverbal task. Neuroimage 2000;11:157–66.

[33] Völlm BA, Taylor AN, Richardson P, Corcoran R, Stirling J, McKie S, et al. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. Neuroimage 2006;29:90–8.

[34] Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 2005;25:1325–35.

[35] Nichols T, Brett M, Andersson J, Wager T, Poline J-B. Valid conjunction inference with the minimum statistic. Neuroimage 2005; 25:653–60.

[36] Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. J Neurol Neurosurg Psychiatry 2007;78:917–28.

[37] Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, et al. Selective frontoinsular von economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cerebral Cortex 2012; 22:251–9.

[38] Olson IR, Plotzker A, Ezzyat Y. The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain 2007; 130(pt 7):1718–31.

[39] Grossman ED, Blake R. Brain areas active during visual perception of biological motion. Neuron 2002;35:1167–75.

[40] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201–15.

[41] Samson D, Apperly IA, Chiavarino C, Humphreys GW. Left temporoparietal junction is necessary for representing someone else's belief. Nat Neurosci 2004;7:499–500.

[42] Hamilton AF, Grafton ST. Goal representation in human anterior intraparietal sulcus. J Neurosci 2006;26:1133–7.

[43] Mar RA. The neural bases of social cognition and story comprehension. Annu Rev Psychol 2011;62:103–34.

[44] Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 2006;129(pt 3):564–83.

[45] Jesso S, Morlog D, Ross S, Pell MD, Pasternak SH, Mitchell DGV, et al. The effects of oxytocin on social cognition and behaviour in frontotemporal dementia. Brain 2011;134:2493–501.