Published in final edited form as:

J Neuropsychiatry Clin Neurosci. 2011 ; 23(1): 74–82. doi:10.1176/appi.neuropsych.23.1.74.

Social Cognition, Executive Functioning, and Neuroimaging Correlates of Empathic Deficits in Frontotemporal Dementia

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Abstract

The authors investigated aspects of interpersonal sensitivity and perspective-taking in relation to empathy, social cognitions, and executive functioning in 26 frontotemporal dementia (FTD) patients. Behavioral-variant FTD (bvFTD) patients were significantly impaired on caregiver assessments of empathy, although self-ratings were normal. Progressive nonfluent aphasia and semantic-dementia samples were rarely abnormal. In bvFTD, empathy ratings were found to be correlated with social cognition and executive functioning measures, but not depression. Voxel-based morphometry revealed that reduced empathic perspective-taking was related to bifrontal and left anterior temporal atrophy, whereas empathic emotions were related to right medial frontal atrophy. Findings suggest that bvFTD causes multiple types of breakdown in empathy, social cognition, and executive resources, mediated by frontal and temporal disease.

Processing-deficits in the interpersonal sphere can constitute presenting symptoms and a prominent dimension of the natural history of brain diseases. Social impairments and their underlying bases have been a longstanding theme in neurobehavioral study of patients with frontal lobe syndromes.^{1–4} These observations have become increasingly important with identification of frontotemporal dementia (FTD).⁵ Progressive social impairments are a major clinical feature of FTD, principally in the subgroup manifesting significant behavioral, personality, and executive-functioning deficits (i.e., behavioral-variant FTD [bvFTD]).^{6–8} In contrast to other prominent neurodegenerative diseases, bvFTD patients do not present with prominent speech, language, or general-knowledge disorders, as in progressive nonfluent aphasia (PNFA) and semantic dementia (SD), nor do they manifest progressive short-term memory deficits, such as in Alzheimer's disease, or progressive motor, apraxia, and sensory symptoms, as in corticobasal syndrome. Hence, their subtle, but progressively disabling, social deficits can go unrecognized or misdiagnosed for years.

Recent investigations of bvFTD have begun to evaluate their underlying deficits by using various correlates of social impairments.^{9–14} In a neural-systems model of social cognition,

we have proposed important interrelationships of social and cognitive domains in a *social executor* framework of deficits in bvFTD,¹⁵ drawing from social-cognitive studies in adult patients with acquired focal lesions of the frontal lobe.^{16–18} Social executors encompass social knowledge *and* executive resources (including self-awareness and self-regulation), as well as motivational and emotional components associated with interpersonal actions. Social knowledge elaborates the store of social perceptions, actions, experiences, and sequences that are bound by learned rules, conventions, and conditional probabilities, typically what is identified as social cognition. In this view, effective utilization of social knowledge is also constrained by several allied processing resources that are specific to the social domain (e.g., theory of mind, empathic sensitivity), by domain-neutral executive resources (e.g., cognitive flexibility, self-awareness, self-regulation), and by motivational and emotional influences that bias social perceptions and actions (e.g., social emotions).^{19–21}

Evidence consistent with this view comes from our previously reported work with bvFTD. These studies showed significant deficits on measures of social knowledge and associated social (e.g., theory of mind, empathy) and executive (e.g., cognitive flexibility, metacognition) processing resources that contribute to social disability. Furthermore, these patients have limited control over the regulation of motivational states, which can manifest along a spectrum from apathy to impulsivity and behavioral disinhibition. We related these deficits to cortical atrophy in a large-scale neural network encompassing at least orbital frontal, medial frontal, and superior temporal regions, more prominently in the right hemisphere.^{12,14,15}

Empathy is an important domain of social emotion and cognition that influences interpersonal judgment, emotions, and behavior.^{22,23} Cognitive (i.e., perspective-taking) and emotional (i.e., sensitivity, attachment) resources may be activated in empathy and serve to foster shared interpersonal experiences and understanding of other's experiences and mental states. Changes in empathy have been noted in clinical descriptions of FTD,⁵ as well as in studies of focal frontal-lobe lesions.^{17,24} A standardized survey of caregivers²⁵ identified cognitive-empathic changes in a frontal-variant FTD sample and decline in both cognitive and emotional empathy in a temporal-variant FTD sample. A second, larger sampling of caregivers reported both cognitive and emotional empathic changes in FTD patients with frontal-related behavioral changes and with features of semantic dementia (SD), although changes were not detected in patients with progressive nonfluent aphasia (PNFA).²⁶ When caregivers rated empathic behaviors pre- versus post-disease onset in a sample of frontal-variant FTD patients, significant decline was detected in both cognitive and emotional empathy.⁹ Hence, we hypothesized that analysis of a standardized behavioral inventory would confirm significant cognitive and emotional empathic deficits in a bvFTD sample, although we were uncertain about empathic changes in an FTD aphasic sample (SD and PNFA), since we have not observed such changes in previous research or in clinical care. Although limited insight into their own social deficits has been documented in previous studies of bvFTD,^{11,12} few studies have specifically compared ratings of empathy in bvFTD patients with the ratings of their caregivers.

Social disorders in bvFTD have been associated with predominantly right-sided pathophysiology.^{27,28} Rankin et al.²⁶ directly related empathy and cortical atrophy in a large group of patients with various neurodegenerative conditions. They reported an association of overall empathy score with atrophy in the right temporal pole, right fusiform gyrus, and the right medial frontal region. In this mixed sample, emotional empathy was related to the right temporal pole, right subcallosal gyrus/caudate, and right inferior frontal gyrus, whereas cognitive empathy also was related to the right temporal pole, right subcallosal gyrus/caudate, and right fusiform gyrus. When subgroups of their sample were examined, total

empathy score was related to the right subcallosal gyrus in bvFTD and to the right temporal pole in SD.

The present study was designed to characterize interpersonal deficits in bvFTD more clearly, by investigating multiple dimensions of empathy from the social executor perspective. Specifically, we investigated empathy-related behavioral changes in FTD samples (bvFTD, PNFA, SD) and healthy-control participants, utilizing patient ratings and caregiver ratings, on a standardized survey scale, the Interpersonal Reactivity Index (IRI).²² We were particularly interested in determining the contribution of social and executive factors to empathic changes, including cognitive (i.e., social perspective-taking) and emotional (i.e., social-emotional concern) aspects of empathic behaviors. We also investigated the neural correlates of empathic deficits in bvFTD by use of voxel-based morphometry. We expected that cognitive and emotional deficits in empathy in bvFTD would be related to distinct impairments of executive resources and emotional knowledge. Moreover, we expected changes in cognitive and emotional forms of empathy to be associated with distinct neural substrates.

METHOD

Subjects

Twenty-six patients were diagnosed according to published criteria for FTD,^{5,29–31} with other dementia causes excluded by clinical exam, blood work, and brain-imaging tests. Informed consent was provided by participants and caregivers according to University of Pennsylvania Institutional Review Board-approved protocol.

Two independent examiners established consensus diagnoses for FTD as well as FTD subgroups, as follows: bvFTD (N=12), PNFA (N=7), and SD (N=7) patients. Participants were alert and cooperative. They were not taking any sedating medications such as benzodiazepines at the time of testing that could interfere with cognitive and social functioning. All bvFTD subjects completed high-resolution T1 brain MRI for voxel-based morphometry analyses. Normal-control (NC) participants (N=16) were chosen to match FTD samples for age, education, and gender, differing only by their higher Mini-Mental State Exam (MMSE) scores from the FTD samples ($p < 0.0001$). The bvFTD sample was also marginally younger than NCs ($p < 0.05$).

Materials and Procedures

Behavioral and Cognitive Measures—Patients and their caregivers (as well as NCs and their spouses or other informant) completed the IRI,²² a standardized, 28-item inventory of empathy that yields a total score, as well as four subscale scores (Perspective-Taking, Fantasy, Empathic Concern, and Personal Distress). Cognitive and emotional aspects of empathy were compared by contrasting the Perspective-Taking and Empathic Concern subscales. A survey of depressive symptoms was undertaken with the Beck Depression Inventory (BDI).

Measures of social cognition and executive functions, as previously reported for FTD samples,^{6,15} are briefly described here and included the following: Cartoon Predictions—a shortened, 10-item version of Form A³² assessed prediction of social consequences. Performance was untimed, after a practice item established that participants understood the task; Theory of Mind—12 vignettes assessed judgment of story facts and first- and second-order beliefs of characters in social situations.³³ Each scenario was presented with Lie and Joke conditions that required contrasting decisions about a main character's first-order beliefs, and the second-order beliefs that another character held of the main character.

Second-order belief questions also required interpretation of whether the character was lying to avoid getting caught or joking to cover up embarrassment. Vignettes were read aloud and concurrently presented in written format. A practice vignette was presented to establish that participants understood the task; Visual Verbal Test—this nonsocial measure of cognitive flexibility and executive resources required abstraction and response-shifting. Stimulus sets were four geometric designs on a single page.^{34,35} Participants categorized three of the designs in two different ways, based on similarity in color, shape, size, or orientation (e.g., 3 designs black, 3 designs triangular). The 10 stimulus sets were preceded by a practice item. First-choice accuracy ranged from 0 to 10, and second-choice accuracy was computed relative to first-choice score (range: 0–100%); Trail-Making Part B—the standard version of this number/letter sequencing and switching task was completed, with scoring of amount of time to completion, up to 300 seconds;³⁶ the Stroop Interference Test—Subjects read aloud 5 columns of 16 color names printed in a colored font that differed from the word (e.g., the word RED printed in a green font). Number of inhibitory errors was computed over 300 seconds.³⁷

Data were statistically evaluated with analysis of variance, post-hoc Scheffé tests, and Pearson correlation analysis for significance.

Imaging Procedure

High-resolution structural MRI images were obtained for bvFTD patients in a Siemens TREO 3T MRI scanner. After rapid sagittal T1-weighted imaging to determine patient position, high-resolution, T1-weighted 3D MPRAGE images were acquired with repetition time (TR) of 1,620 msec., echo time (TE) of 30 msec., 1-mm. slice thickness, flip angle of 15°, matrix size of 192×256, and rectangular field of view giving an in-plane resolution of 1.0×1.0 mm. Images were processed as follows: First, novel symmetric diffeomorphic brain volumes were registered in SPM99,³⁸ using 12-parameter affine registration, nonlinear registration using 12 nonlinear iterations, and 7×8×7 basis functions. Brains were normalized to the T1 template of 305 averaged brain volumes with standardized brain coordinates using a high-dimensional normalization procedure.³⁹ Brain volumes were segmented into four tissue types (gray-matter, white-matter, cerebrospinal fluid [CSF], other). The segmentation algorithm in SPM99 calculates a Bayesian probability for each tissue-type voxel in the volume, based on a priori MRI information. We inspected each slice of each segmented volume to ensure that no voxels from the dural sinuses or adjacent non-brain structures were misclassified as gray matter. Using SPM99, the gray-matter volume was smoothed with a 12-mm FWHM Gaussian filter to minimize individual gyral variations.

Voxel-based morphometry (VBM) in SPM99 analyzed brain volumes.⁴⁰ A proportional-analysis threshold included only voxels with 40% or more of the grand mean value. Implicit masking was used to ignore zeros, and global calculation was based on the mean voxel value. SPM99 analyses included a two-sample *t*-test routine to compare the gray-matter volume of bvFTD patients to 12 healthy, age-matched control subjects. Statistical threshold for atrophy studies relative to controls was set at $p < 0.0001$. We did not correct for multiple comparisons because of the hypothesis-driven nature of the analyses. Moreover, the small size of the voxels would make Bonferroni-like statistical correction too conservative. Instead, clusters of 100 or more adjacent voxels were considered, reflecting a statistically robust effect, exceeding $p < 0.05$, corrected for multiple comparisons in this neuroanatomic distribution.⁴¹ Regression-analyses related IRI Perspective-Taking and Empathic Concern scores to gray-matter atrophy derived from contrast of cortical atrophy in the bvFTD group with the control subjects. Statistical threshold for these analyses was set at $p < 0.001$, uncorrected, requiring >100 adjacent voxels per cluster.

RESULTS

Empathy Scores

Patient and caregiver (as well as control participant and close informant) ratings of empathy are summarized in Table 1. Caregiver ratings of patients revealed a marked drop in Total scale score for the bvFTD sample only ($p < 0.02$, as compared with other samples). Analysis of IRI factors indicated that only the bvFTD sample was rated by their caregivers as significantly lower in both Perspective-Taking (PT; $p < 0.006$) and Empathic Concern (EC; $p < 0.009$). Self-ratings of empathy-related behaviors did not differ among FTD subgroups and controls, except that PNFA participants generated high Personal Distress (PD) scores (as did their caregivers), possibly related to their prominent disorder of effortful speech. Among the bvFTD patients, caregiver ratings on PT and EC subscales approached a significant correlation ($r = 0.43$; $p = 0.086$), suggesting only a modest relationship between these two scales. Because of the marked deficits in the bvFTD sample and the absence of any consistent deficits in the SD and PNFA samples, further analyses (below) were focused on the bvFTD subgroup.

IRI results for the bvFTD sample showed a difference between their self-ratings on the Total empathy score and the ratings of their caregivers ($p < 0.05$). We also observed trends toward large discrepancies between higher patient and lower caregiver ratings on PT and EC subscales ($0.05 > p < 0.10$). This is consistent with the limited self-awareness and insight demonstrated in previous studies of these patients. No other significant discrepancies emerged in comparisons of patients with controls and their informants.

Correlations With Social-Cognitive, Executive Functioning, and Emotion Measures in bvFTD

PT scores rendered by caregivers were positively correlated with social cognition measures in bvFTD patients (Theory of Mind: $r = 0.54$ and Cartoon Predictions: $r = 0.672$; $p < 0.05$, respectively), but EC changes were not related to these measures of social cognition. Both PT and EC scores were significantly correlated with executive measures of mental flexibility (Visual-Verbal Test: $r = 0.72$ and 0.94 , $p < 0.05$, respectively). Neither PT nor EC scores from caregivers of bvFTD patients were correlated with depression scores.

Voxel-Based Morphometry Analyses in bvFTD

Significant relationships were uncovered between cortical atrophy on MRI scan and changes in PT and EC for the bvFTD subgroup (Figure 1). Atrophic areas related to empathic PT changes included a large expanse of right dorsolateral prefrontal cortex, extending from pre-motor cortex to the frontal pole, smaller portions of the right parietal lobe and left supplementary motor area, left superior temporal cortex and temporal pole, and subcortical structures (right amygdala and left caudate; see Table 2). Areas related to EC changes included right superior medial prefrontal cortex (Brodmann's Area 8) and left supplementary motor cortex.

DISCUSSION

Results support a model of multiple associations among social-cognition, empathy, and executive functioning resources that break down in multivariate, convergent fashion in FTD patients with prominent social and executive impairments. Standardized caregiver ratings of empathy-related behavioral changes in FTD identified marked decrements in both cognitive (i.e., perspective-taking) and emotional (i.e., emotional concern) aspects in bvFTD patients. These results parallel the findings of previous work.^{9,26} The lack of empathy in bvFTD is extraordinarily disturbing to caregivers.¹⁴ Such changes were not evident in the caregiver

ratings for the PNFA and SD samples, supporting the specificity of the results for the consensus diagnosis of bvFTD disorders and presumed frontal-limbic involvement. The lack of observed empathic changes in SD patients, as seen by Rankin et al.,²⁶ may be related in part to an ascertainment bias. That is, patients referred to our center may have comparatively less prominent social features than patients referred to the center where Rankin et al. completed their study. Additional multicenter studies are needed to resolve issues such as the nature and severity of social disorders in patients with progressive aphasia.

Observations of empathy changes similar to our study findings underscore the profound and wide-ranging empathic deficits in bvFTD, involving both cognitive and emotional forms of empathy. Also, we sought to investigate the basis for the empathic deficit in bvFTD by analyzing close associations. According to the social executor model, social knowledge as well as social and domain-neutral executive resources contribute to complex processes like empathy. From this perspective, we were particularly interested in determining whether social and executive resources are related to empathic limitations in bvFTD. We found that decline in the cognitive or perspective-taking aspects of empathy correlated significantly with social-cognitive (i.e., Theory of Mind and Cartoon Predictions) and executive (i.e., Cognitive Flexibility) measures. Decline in emotional empathy correlated only with executive functioning. These observations suggest an ideational association between social-cognitive resources and empathy, and, moreover, suggest that resources may be shared across social-interpersonal and executive cognitive processing. Such correlations have been suspected in bvFTD patients on the basis of results of clinical studies, and overlapping pathophysiology that has been identified in focal frontal lesion cases¹⁷ and in previous assessments of social cognition in bvFTD.^{12,15} For example, during a three-alternative, forced-choice, social problem-solving task, we identified a significant deficit in bvFTD. Correlational analyses revealed that performance was related to theory of mind, empathy, and cognitive flexibility measures.¹² A regression analysis demonstrated that the measure of cognitive flexibility accounted for the largest portion of the variance in social judgment performance. Observations such as these and the findings of the present study provide support for the social executor model.

Previous work has examined the relationship between disorders of social functioning and executive-resource limitations in bvFTD. The results have been inconsistent across studies, and likely related to differences in the tasks used to probe empathy and cognition in the patients and caregivers being probed. Similar to Rankin and colleagues, we used the IRI to determine whether distinct forms of empathy may be identified in bvFTD. We found confirmatory evidence that the correlation between cognitive and emotional forms of empathy can make it difficult to dissociate these two easily in bvFTD patients. On the other hand, the subgroup of patients with bvFTD have significant executive-function deficits,^{42,43} and it is reasonable to propose that the social disorder in bvFTD is due in part to their executive-resource limitations. Although we demonstrated this in our previous assessments of social problem-solving and self-awareness,^{12,15} such associations between social-emotional and executive-cognitive functioning may not have been seen in other work because of limited ascertainment of cognitive measures, such as assessment of a partial range of relevant measures. For example, Lough and coworkers^{9,41} examined a limited range of executive measures requiring cognitive estimation, but did not assess measures of mental flexibility that may be a more pertinent cognitive component of empathy. Alternately, there may be qualitative or quantitative differences between the patients assessed in different studies. There may be differences in the severity of disease across bvFTD patients participating in different studies. This is difficult to ascertain since there is no universally accepted measure of severity for patients with FTD. On the basis of disease duration, our patients were mildly-to-moderately impaired. A second, patient-related issue is concerned with the qualitative nature of bvFTD. Previous criteria were not necessarily

reliable at identifying these patients,⁴⁵ and there is an ongoing effort to improve diagnostic criteria for bvFTD.^{13,46} Moreover, the bvFTD phenotype does not differentiate between the subgroup of FTD patients with predominantly frontal disease and predominantly temporal disease. Recent work has associated social knowledge more prominently with right anterior temporal regions,^{20,47} although resource-dependent social functioning may be mediated more by the right frontal lobe. It may be that patients participating in studies are not equated in the burden of frontal and temporal disease. From this perspective, the presence of frontal disease critically interferes with implementing social knowledge in a flexible and adaptive manner in social situations, and the patients we examined in the present study have sufficient frontal disease to interfere with this component of empathy.

Lough et al.⁹ emphasized the importance of the informant report for detection of empathy-related changes in FTD, since the comparison of patient and caregiver behavioral ratings provides important observations about the degree of self-awareness changes in FTD. The degree of discrepancy we evaluated was based on comparison with healthy-controls and their informants, ensuring a conservative analysis that considered naturally-occurring differences between participants and their informants. Furthermore, PNFA and SD samples showed virtually no significant discrepancies from their informants. The single exception was higher Personal Distress ratings in PNFA patients, also identified by their informants, and this may have been related to their highly frustrating speech impairments. It is noteworthy that bvFTD patients and their caregivers appeared to agree on their normal range of Personal Distress ratings. This may reflect the fact that the patients had little insight into their difficulties and thus were not evidently distressed, resembling control subjects who were not distressed, in the context of having no neurodegenerative disease. The predominant pattern of the bvFTD patients was not to identify any empathy-related behavioral changes, in marked contrast to caregiver observations. This loss of social self-awareness, which is a key domain of social executors,¹⁸ is consistent with systematic observations from other measures,^{11,12} as well as clinical correlation to right-frontal hypoperfusion.⁴⁸ Thus, bvFTD patients exhibit not only significant social-cognitive, executive, and empathic alterations, but also a lack of awareness of their social insensitivity.

As might be expected on the bases of lesion and functional-imaging studies,^{23,49} cognitive and emotional empathic changes were associated with pathophysiology in different cortical and subcortical regions. Empathic perspective-taking was correlated with widespread areas of the right dorsolateral prefrontal cortex, extending from premotor to polar regions, left superior mesial prefrontal-premotor cortices, right parietal regions, and left superior temporal gyrus and temporal pole, as well as subcortical areas of the right amygdala and left caudate. These cortical areas have been associated with theory-of-mind processing, executive functions of planning, cognitive flexibility and foresight, social knowledge, multiple cognitive aspects of empathy (e.g., valuation of thoughts, social emotions, one's own behavior and the behavior of others, recognition of alternative actions), and cognitive-emotional integration.^{50–55} In contrast, empathic emotion was correlated with more restricted right superior mesial cortex changes, an area implicated in shared self-other representations, as well as self-referencing of emotion and volition.^{49,56} These results are also consistent with the suggestion by Mendez⁵⁷ that the decline in moral judgment in FTD patients with frontal-variant symptoms may arise in part from an empathic loss in emotionally identifying with others. In the only other study to date examining anatomical correlates of empathy changes in bvFTD, a combined empathy score was related to structural integrity of the right subcallosal gyrus, with scores from a larger, mixed neurodegenerative disease group associating empathy with atrophy in right frontal-temporal regions, particularly the temporal pole, subcallosal gyrus, and caudate and fusiform gyrus.²⁶ Our results suggested distinct differences between anatomical correlates for empathic perspective-taking and empathic emotional concern, although both showed strong frontal-

lobe correlations. These cognitive and emotional empathic changes in our bvFTD sample are consistent with extensive literature based on clinical lesion analysis, functional brain imaging, and connectional anatomy in nonhuman primates, indicating that the prefrontal regions are involved in cognitive and emotional processing, and, quite likely, complex integration of cognition and emotion.^{20,23,53,58–62}

The findings confirm and extend the observations regarding multiple behavioral, cognitive, and social-emotional symptoms and deficits in bvFTD patients. The results support the conclusion that several of these are interacting and synergistic effects of pathophysiology in the frontal, anterior temporal, and interconnected subcortical regions in this clinical group, giving rise to these clinical deficits. The measures used appear to provide both sensitive and quantitative assays of fronto-temporal functions affected in bvFTD patients, and these may constitute informative screening instruments.

Acknowledgments

This work was supported in part by NIH grants AG17586, AG15116, NS44266, and NS53488.

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FIGURE 1.
Areas of Significant Cortical Atrophy Correlated With Caregiver Ratings of bvFTD Patients' (A) Empathic Perspective-Taking, and (B) Empathic Emotional Concern

TABLE 1

Interpersonal Reactivity Index Empathy Scores for FTD Clinical Subgroups

Interpersonal Reactivity Index	bvFTD		PNFA		SD		Controls	
	Self	Caregiver	Self	Caregiver	Self	Caregiver	Self	Caregiver
PT	15.64	6.83 *	27.80	23.37	14.14	10.38	20.62	15.56
FS	10.55	6.58 *	17.53	13.14	10.71	8.88	13.59	11.56
EC	18.45	11.67 *	26.63	23.60	21.71	18.25	19.78	18.22
PD	10.82	11.75	23.80 *	17.31 *	13.00	10.63	9.80	8.44
Total	55.45	36.83 *	60.91	54.68	59.57	48.13	56.20	53.78

The Interpersonal Reactivity Index generates a Total score and the following subscale scores: PT: Perspective-Taking; FS: Fantasy Scale; EC: Empathic Concern; PD: Personal Distress.

bvFTD: behavioral variant frontotemporal dementia; PNFA: progressive nonfluent aphasia; SD: semantic dementia.

* Significant difference from control subjects ($p < 0.05$).

TABLE 2

Voxel-Based Morphometry Results in the bvFTD Sample, Showing Areas of Atrophy Significantly Correlating With Empathic Perspective-Taking and Empathic Emotional Concern Ratings by Caregivers

Anatomic Locus	Coordinates			Z-score
	X	Y	Z	
Perspective-Taking				
R Prefrontal-Premotor (6/24)	6	−7	48	3.49
R Precuneus (8/9)	14	−40	54	4.54
R Amygdaloid Complex	38	5	−22	3.52
R Angular (39)	53	−62	34	4.57
R Parietal (31)	6	−63	23	3.92
L Supplementary Motor Area (6/24)	−6	7	57	3.45
L Superior Temporal (38/22)	−32	2	−34	3.70
L Caudate	−16	23	3	3.68
Empathic Concern				
R. Medial Frontal (8)	4	50	38	3.50
L Supplementary Motor Area (6)	−14	13	56	4.19