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Neuroanatomical correlates of emotional blunting in behavioral variant frontotemporal dementia and early-onset Alzheimer's disease

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Abstract

Background—Emotional blunting is a characteristic feature of behavioral variant frontotemporal dementia (bvFTD) and can help discriminate between patients with bvFTD and other forms of younger-onset dementia.

Objective—We compared the presence of emotional blunting symptoms in patients with bvFTD and early-onset Alzheimer's disease (AD), and investigated the neuroanatomical associations between emotional blunting and regional brain volume.

Methods—Twenty-five individuals with bvFTD (n=11) and early-onset AD (n=14) underwent magnetic resonance imaging (MRI) and were rated on symptoms of emotional blunting using the Scale for Emotional Blunting (SEB). The two groups were compared on SEB ratings and MRI-derived brain volume using tensor-based morphometry (TBM). Voxel-wise linear regression was performed to determine neuroanatomical correlates of SEB scores.

Results—The bvFTD group had significantly higher SEB scores compared to the AD group. On MRI, bvFTD patients had smaller bilateral frontal lobe volume compared to AD patients, while AD patients had smaller bilateral temporal and left parietal volume than bvFTD patients. In bvFTD, SEB ratings were strongly correlated with right anterior temporal volume, while the association between SEB and the right orbitofrontal cortex was non-significant.

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Conclusions—Symptoms of emotional blunting were more prevalent in bvFTD than early-onset AD patients. These symptoms were particularly associated with right-sided atrophy, with significant involvement of the right anterior temporal region. Based on these findings, the SEB may be a useful diagnostic instrument for identifying a key clinical feature of bvFTD and appears to measure symptoms that are localized to the right anterior temporal lobe.

Keywords

Frontotemporal Dementia; Alzheimer's Disease; Early Onset; Magnetic Resonance Imaging; emotional blunting

Introduction

The behavioral variant of frontotemporal dementia (bvFTD) is one of the most common dementias affecting a younger population, with age of onset typically in the 50's [1]. It is characterized by profound and progressive changes in personality and behavior, including behavioral disinhibition, apathy, emotional blunting, perseverative behaviors, and dietary changes, as well as frontal-executive deficits on neuropsychological testing [2]. Although some bvFTD patients demonstrate neuropsychological impairments on tasks of attention, working memory, and other executive functions [3], many demonstrate relatively intact cognitive functioning in early stages of the disease [4]. Therefore, assessment of behavioral disturbances are more sensitive in identifying and diagnosing the disorder in earlier stages, and can help to discriminate these patients from those with other forms of dementia, such as Alzheimer's disease (AD), who often have relatively preserved social and behavioral functioning in early stages [5].

One hallmark symptom of bvFTD that often precedes significant cognitive decline is emotional blunting. Emotional blunting, which is described as a loss of empathy and emotional warmth [6], can be especially disturbing for family members of bvFTD patients who appear to become emotionally detached and apathetic towards their loved ones. However, symptoms of emotional blunting often develop insidiously and can be misinterpreted or misdiagnosed as a psychiatric disorder [7], making it difficult to reliably assess and identify emotional blunting as a symptom of an underlying neurological disorder.

The Scale for Emotional Blunting (SEB) [8] is a brief measure that rates symptoms of emotional blunting across three domains: pleasure-seeking behavior, affective blunting, and cognitive blunting. It has been shown to have good inter-rater reliability [9], and has been used in prior studies to show that bvFTD patients demonstrate significantly more symptoms of emotional blunting than patients diagnosed with AD [9, 10]. A recent meta-analysis found that the SEB was one of the most sensitive measures for discriminating those with bvFTD from patients with AD [11].

Neuroanatomically, bvFTD patients most often demonstrate significant atrophy of frontal regions, including the anterior cingulate, ventromedial and orbitofrontal cortex [12–15], and some additionally show secondary involvement of the anterior temporal regions [16, 17]. Prior studies have shown that loss of empathy, in particular, may be more specifically associated with the right anterior temporal region [18, 19]. In the current study, we used

tensor-based morphometry (TBM) to examine the neuroanatomical correlates of symptoms of emotional blunting on the SEB in patients with bvFTD and AD. To our knowledge, this is the first study examining the association between SEB ratings and regional brain volume on magnetic resonance imaging (MRI).

Materials and Methods

Participants

The current study included 25 patients (11 diagnosed with bvFTD and 14 with early-onset AD), ranging in age from 42 to 76, who were recruited from the Neurobehavior Clinic at UCLA. The diagnosis of bvFTD was based on International Consensus Criteria for probable bvFTD [2], which include disinhibition, apathy, loss of empathy, compulsive-like behaviors, dietary changes, and disproportionate executive dysfunction on neurocognitive testing. The diagnosis of early-onset AD was determined by the National Institute of Communicable Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for clinically probable AD [20], with the additional requirement of age of symptom onset prior to age 65. Individuals with major medical illnesses (except hypertension or diabetes) or psychiatric illnesses not due to the dementia process were excluded from the study. All subjects received written and oral information about the study and signed written informed consents approved by the local institutional review board prior to study participation.

Scale of Emotional Blunting (SEB)

Symptoms of emotional blunting were rated by the same examiner using the Scale for Emotional Blunting (SEB; [8]), an observer rating scale with 16 items each assessed on a three-point scale (0 = "condition absent," 1 = "slightly present or doubtful," 2 = "clearly present"). Items assess symptoms across 3 domains: affect, behavior, and thought content. Characteristic items included "absent, shallow, incongruous mood," "expressionless face," "unvarying monotone voice," and "indifference/lack of affection for family, friends." The sum score of all 16 SEB items was used as the index of emotional blunting.

MRI acquisition and pre-processing

All subjects were scanned in the same 1.5 Tesla Siemens MRI scanner with the same imaging protocol. High-resolution T1-weighted 3D MRI scans were acquired in the coronal plane using a 3-D MP-RAGE sequence. The following scanning parameters were used: TR/TE/NEX = 2000/2.89/1; TI = 900ms, flip angle = 8°, slice thickness = 1mm, 25.6 cm field of view, 256 × 256 acquisition matrix, voxel size = 1.0×1.0×1.0 mm³. An automated Brain Surface Algorithm (BSE) from BrainSuite [21] was applied, along with manual editing to generate a deskulled brain volume with the scalp, dura, and meninges removed. All scans were linearly registered to the stereotaxic space defined by the International Consortium for Brain Mapping (ICBM) with a 9-parameter transformation, and were resampled in an isotropic space of 230 voxels for each axis (x, y, and z) with a final voxel size of 1 mm³.

Tensor-based Morphometry (TBM)

To quantify 3D patterns of volumetric brain differences for each subject, an individual difference map (Jacobian map) was computed by non-linearly registering each individual scan to a template brain with an inverse-consistent elastic intensity-based registration algorithm, with a built-in smoothing kernel, driven by a mutual information-based cost function (3DMI), which has been previously described in Leow et al. [22]. A map of the Jacobian determinants was computed from the gradient of the deformation field to illustrate regions of relative volume differences between each individual and the template. All results and statistical analyses were based on the Jacobian maps.

Statistical Analyses

To illustrate systematic group differences in brain volume, we constructed voxel-wise statistical maps based on the Student's *t* statistic. Regions of interest (ROI) were manually hand-traced on the template. The Jacobian maps of each group were compared using two-sample *t* tests to assess the overall significance of group differences at the whole-brain level and within each ROI, corrected for multiple comparisons using permutation tests.

A voxel-wise linear regression was performed on the Jacobian maps, yielding 3D statistical maps of the association between tissue volume and SEB ratings. Mean Jacobian values within select ROIs (orbitofrontal cortex; anterior temporal lobes) were computed for each subject to provide a numeric summary of regional volume. Partial Pearson correlations, adjusted for age, were computed to examine the association between these regional volume measures and SEB ratings. All algorithms used in neuroimaging analysis, including TBM Jacobian brain maps, voxel-wise statistical tests, and ROI-specific mean Jacobian values, were developed at the Laboratory of NeuroImaging (LONI) and have been successfully used in previous studies measuring brain volumetric changes in neurodegenerative disorders [23, 24].

Results

Demographics

The demographic characteristics of the current sample are summarized in Table 1. The two diagnostic groups did not differ significantly on any of the demographic variables. In the combined sample, SEB ratings were not significantly associated with age, education, or MMSE scores (age $p = .15$, education $p = .85$, MMSE $p = .74$), and did not differ by gender ($p = .43$). No significant associations were found when each group was examined independently (FTD: age $p = .74$, education $p = .36$, MMSE $p = .64$, gender $p = .78$; AD: age $p = .69$, education $p = .51$, MMSE $p = .34$, gender $p = .82$).

Neuroanatomical differences between diagnostic groups

Jacobian maps of the bvFTD and AD patients were compared using a voxel-wise *t*-test to yield the statistical maps shown in Figure 1. In Figure 1a, the AD group demonstrated significantly smaller brain volume than the bvFTD group in the bilateral temporal lobes ($p = .009$), including the hippocampus ($p = .031$), as well as the left parietal region ($p = .025$). The bvFTD group exhibited significantly smaller brain volume than the AD group in the bilateral

frontal lobes ($p=.019$, Figure 1b). The bvFTD group also demonstrated smaller right anterior temporal lobe volume than the AD group, but the difference was non-significant after correcting for multiple comparisons.

SEB ratings and Neuroanatomical correlates

The bvFTD patients had higher ratings on the SEB scale (indicating more symptoms of emotional blunting) compared to the AD patients in both their Total scores, and on each individual subscale (Table 2). A voxel-wise linear regression of the Jacobian maps with total SEB scores was performed for the combined sample, controlling for age and diagnosis. The resulting statistical map (Figure 2) revealed clusters of voxels in the right anterior temporal lobe (ATL) and right orbitofrontal cortex (OFC) that were significantly ($p<.05$) associated with total SEB scores. However, partial correlations between SEB scores and mean Jacobian values for each ROI, adjusted for age and diagnosis, did not reach statistical significance (right OFC $r = -.32$, $p = .13$; right ATL $r = -.29$, $p = .18$; Table 3).

Independent examination of each group revealed that the restricted range of scores obtained on the SEB by AD patients (range=0–3) resulted in little or no association between SEB scores and brain volume in the AD group (right OFC $r = -.18$, $p = .57$; right ATL $r = .05$, $p = .87$). Analysis of the FTD group alone (Figure 3), however, showed a significant negative correlation between total SEB scores and the right anterior temporal lobe ($r = -.77$, $p = .01$), indicating more symptoms of emotional blunting were associated with smaller right anterior temporal volume. There was also a negative correlation between total SEB scores and the orbitofrontal region, but the correlation did not reach statistical significance ($r = -.36$, $p = .31$). Partial correlations between SEB subscale scores (Affect, Behavior, Thought) and ROI-specific mean Jacobian values similarly revealed significant associations between all 3 subscales and the right anterior temporal lobe (SEB-Affect $r = -.68$, $p = .03$; SEB-Behavior $r = -.65$, $p = .04$; SEB-Thought $r = -.81$, $p = .004$). Correlations between SEB subscale scores and the right orbitofrontal cortex were non-significant (Table 4).

Discussion

We examined symptoms of emotional blunting in two groups of younger onset dementia (bvFTD and early-onset AD) and found that 1) bvFTD patients exhibit significantly more emotional blunting than similar-age patients with AD and 2) symptoms of emotional blunting in bvFTD patients were correlated strongly with right anterior temporal lobe volume. Prior studies [25–27] have shown that assessment of personality and behavioral changes can be sensitive in distinguishing bvFTD from AD, particularly in early stages of the disease [28]. Two studies [9, 10] used the SEB specifically to effectively discriminate between patients with bvFTD and AD. Consistent with these previous findings, the bvFTD patients in our sample had significantly higher ratings of emotional blunting on the SEB compared to the AD patients, lending further support to the utility of using the SEB to identify a diagnostic clinical feature of bvFTD.

The personality and behavioral changes typically observed in bvFTD, including apathy, disinhibition, and loss of empathy, have most often been associated with atrophy of frontal regions, including the anterior cingulate, ventromedial and orbitofrontal cortex [12, 15], with

secondary involvement of anterior temporal regions [16, 17]. Thus, when overall brain volume was compared between the bvFTD and AD groups in our sample, bvFTD patients unsurprisingly showed significantly more atrophy in the bilateral frontal lobes. However, although the bvFTD group exhibited more frontal atrophy overall, their symptoms of emotional blunting were most strongly correlated with the right anterior temporal lobe while the orbitofrontal region showed weaker non-significant associations which were still greater on the right than the left.

Prior research has shown more prominent involvement of the right hemisphere in the manifestation of social and emotional dysfunction in bvFTD [13, 14]. Symptoms of apathy, disinhibition, aberrant motor behavior, and appetite/eating changes were associated with atrophy of the right anterior cingulate, right ventromedial prefrontal cortex, right orbitofrontal cortex and right anterior insula [13]. Mychack and colleagues [29] found that even among FTD patients, those with predominantly right-sided hypoperfusion on brain imaging were more likely to exhibit “socially undesirable behaviors” as an early symptom compared to those with more left-sided hypoperfusion. Furthermore, while symptoms of apathy and dietary changes have been more often associated with orbitofrontal and ventromedial frontal dysfunction [14, 15], symptoms involving emotion processing, including emotional blunting and emotion recognition, have additionally been correlated with the right anterior temporal region [30]. In the current study, emotional blunting symptoms were most strongly associated with right anterior temporal volume, showing remarkable specificity in the neuroanatomical localization of symptoms assessed by the SEB. Other studies have reported more variable associations that include right frontal regions in addition to the anterior temporal lobe [31]

Loss of empathy, in particular, has been studied extensively by Rankin and colleagues [32], who proposed that the cognitive and emotional components of empathy may each be mediated by different neuroanatomical structures that together make up an “empathy circuit.” Specifically, they found that patients with bvFTD and semantic dementia (SD) both showed deficits in cognitive empathy, which includes aspects of attention, perspective-taking, and abstract reasoning, while emotional empathy, which includes emotion recognition and emotional responsiveness, was impaired only in SD patients. The bvFTD patients, who tend to show less anterior temporal lobe damage than SD, had preserved functioning on measures of emotional empathy, suggesting that emotional empathy may be more strongly correlated with anterior temporal structures while the cognitive components of empathy may be more mediated by frontal structures that are damaged in both bvFTD and SD. The anterior temporal region also contains structures, like the amygdala, that mediate the recognition and expression of emotions. Damage to the amygdala has been associated with deficits in emotional comprehension [33] and impaired recognition of social emotions [34], which likely contributes to the relationship between the anterior temporal region and emotional empathy.

Although the SEB does not explicitly differentiate between aspects of cognitive versus emotional empathy, the Affect and Behavior subscales consist of items that reflect more emotional aspects of empathy, such as emotional responsiveness and the expression of emotional states, while the Thought subscale addresses symptoms of indifference or

unconcern, which may at least in part be associated with deficits in cognitive components of empathy such as attention or perspective-taking. However, we found that all three subscales were individually correlated with right anterior temporal volume, and thus all contributed to the overall association between the SEB total scores and the right anterior temporal lobe. Correlations with the right orbitofrontal cortex were non-significant in all three subscales.

This study has several limitations. First, as the diagnosis of both patient groups were based on clinical criteria [2, 20], their definitive diagnosis and underlying histopathology remain uncertain. Second, considering the relatively small size of our study sample, the findings reported here should be confirmed through replication in a larger, independent sample. In addition, the cross-sectional design of our study limits our ability to draw conclusions regarding the longitudinal progression of atrophy and requires caution against implying any causal relationships from the association between right anterior temporal volume and emotional blunting. Finally, because our sample is mostly comprised of Caucasian participants, the present findings may not be generalizable to other ethnic groups.

In summary, to our knowledge this is the first study examining neuroanatomical correlates of emotional blunting symptoms on the SEB in bvFTD. We found a striking association between SEB ratings and right anterior temporal lobe volume. These results confirm and strengthen previously reported findings demonstrating a relationship between empathy and the right anterior temporal region. Patients with bvFTD can exhibit variable presentations of the disease, including those with more positive symptoms such as disinhibited behavior, impulsivity and loss of social decorum, as well as those who exhibit more negative symptoms such as apathy, emotional blunting and lack of initiative. Prior research has suggested that each of these symptoms may be localized to specific neuroanatomical regions and/or neural networks. The specificity of the present findings lends further support to the neuroanatomical localization of different presenting symptoms in bvFTD, and suggests that the SEB may be a useful instrument for identifying signs of emotional dysfunction that can facilitate more accurate diagnosis of bvFTD.

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Figure 1.

Statistical group comparisons of Jacobian maps of bvFTD and AD patients: resulting maps show regions where AD group had smaller volume compared to bvFTD (1a), and regions where the bvFTD group had smaller volume than the AD patients (1b).

Figure 2.
Voxel-wise regression of SEB Total scores in entire sample, controlling for age and diagnosis: SEB scores correlate with right anterior temporal lobe, and right orbitofrontal.

Figure 3.
Voxel-wise regression of SEB Total scores in FTD group: SEB scores correlate with right anterior temporal lobe.

Table 1

Demographic and clinical characteristics of bvFTD and AD groups

Demographic variables	bvFTD (n=11) Mean (s.d.)	AD (n=14) Mean (s.d.)	t or χ^2	p
Age, <i>years</i>	63.1 (11.0) range=42–76	57.4 (4.5) range=49–63	1.60	.14
Education, <i>years</i>	15.5 (2.3) range=12–20	16.1 (2.0) range=12–18	0.80	.43
Gender, <i>m/f</i>	5m/6f	4m/10f	0.76	.38
Race, % <i>white</i>	82%	93%	0.71	.40
Clinical variables				
Age at onset	58.8 (10.9) range=36–74	53.2 (5.8) range=43–63	1.65	.11
Years since onset	4.3 (3.8) range=2–15	4.2 (2.5) range=0–9	0.05	.96
MMSE	24.1 (4.5) range=16–30	23.7 (4.8) range=15–29	0.21	.84

MMSE, Mini-Mental State Examination

Table 2

Scale for Emotional Blunting (SEB) Scores of bvFTD and AD groups

SEB scores	bvFTD (n=11) (Mean (s.d.))	AD (n=14) Mean (s.d.)	F _{1,22}	p
Total	10.6 (8.7) range=1–28	1.1 (1.0) range=0–3	12.6	.002
<i>Affect</i>	2.5 (2.5)	0.2 (0.6)	6.6	.018
<i>Behavior</i>	4.7 (3.7)	0.5 (0.7)	14.4	.001
<i>Thought</i>	3.4 (3.4)	0.3 (0.6)	10.6	.004

Table 3

Partial Pearson correlations of Total SEB scores with Regions of Interest

Regions of Interest	Combined Sample <i>Adjusted for age, diagnosis</i>		AD <i>Adjusted for age</i>		bvFTD <i>Adjusted for age</i>	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Orbitofrontal cortex (OFC)	−0.26	0.24	−0.02	0.96	−0.29	0.43
Left OFC	−0.17	0.43	0.14	0.66	−0.21	0.57
Right OFC	−0.32	0.13	−0.18	0.57	−0.36	0.31
Anterior temporal lobe (ATL)	−0.06	0.79	−0.11	0.73	−0.13	0.72
Left ATL	0.17	0.44	−0.25	0.42	0.33	0.35
Right ATL	−0.29	0.18	0.05	0.87	−0.77	0.01

SEB, Scale for Emotional Blunting

Table 4
Partial Pearson correlations of SEB subscale scores with Regions of Interest in bvFTD group, adjusted for age.

Regions of Interest	Affect		Behavior		Thought	
	r	p	r	p	r	p
Orbitofrontal cortex (OFC)	-.35	.32	-.23	.53	-.25	.49
Left OFC	-.30	.40	-.14	.70	-.18	.63
Right OFC	-.40	.26	-.31	.38	-.32	.37
Anterior temporal lobe (ATL)	-.21	.57	.07	.86	-.26	.47
Left ATL	.17	.64	.50	.14	.19	.61
Right ATL	-.68	.03	-.65	.04	-.81	.004

SEB, Scale for Emotional Blunting