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Voxel-based morphometry in patients with obsessive-compulsive behaviors in behavioral variant frontotemporal dementia

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Abstract

Background—Obsessions and compulsive (OC) behaviors are a frequent feature of behavioral variant frontotemporal dementia (bvFTD), but their structural correlates have not been definitively established.

Methods—Patients with bvFTD presenting to the Mayo Clinic Alzheimer's Disease Research Center were recruited. Each patient's caregiver was given the Yale-Brown Obsessive-Compulsive scale (YBOCS) to document the type and presence of OC behaviors and to rate their severity. All subjects underwent a standardized MRI which was evaluated using VBM. 17 patients with bvFTD were recruited and 11 were included in the study and compared to 11 age and gender matched controls. Six were excluded for lack of MRI at time of survey or a pre-existing neurodegenerative condition.

Results—Nine of the 11 reported OC behaviors, with the most frequent compulsions being checking, hoarding, ordering/arranging, repeating rituals, and cleaning. In the VBM analysis, total YBOCS score correlated with grey matter loss in the bilateral globus pallidus, left putamen, and in the lateral temporal lobe, particularly the left middle and inferior temporal gyri ($p < 0.001$ uncorrected for multiple comparisons).

Conclusions—Obsessive-compulsive behaviors were frequent among these patients. The correlation with basal ganglia atrophy may point to involvement of frontal subcortical neuronal networks. Left lateral temporal lobe volume loss likely reflects the number of *MAPT* mutation patients included but also provides additional data implicating temporal lobe involvement in OC behaviors.

Keywords

Frontotemporal dementia; magnetic resonance imaging; obsessive behavior; compulsive behavior

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Introduction

Compulsive and stereotyped behaviors are frequently observed in frontotemporal dementia (FTD). A 1994 autopsy case study described typical obsessive compulsive (OC) behavior in a 34 year-old FTD patient with caudate atrophy (1). A literature review that same year noted that 78% of pathologically proven FTD had repetitive behaviors (2). Another study noted that compulsive behaviors were present in 38% of FTD patients at presentation and only 10% of AD patients (3).

Prior studies addressing compulsive behaviors in FTD have shown inconsistent localization. A case report showed caudate atrophy in one patient (1), a review suggested damage to frontal lobe, caudate, and globus pallidus may be responsible (2), and another study showed no significant neuroimaging correlate of stereotypical behaviors, though all with stereotypies had orbitofrontal damage (4). A voxel-based morphometry (VBM) study of stereotypies in FTD found that those with stereotypies had greater striatal volume loss than those without (5). The applicability of studies including stereotypies to complex compulsive behaviors is unclear, as they may have different anatomic correlates. Other studies suggest that temporal atrophy is key in compulsive behavior (6-8).

There are few reports applying volumetric techniques to structural imaging to provide a structural explanation of the mechanism of compulsive features in neurodegenerative disease. The aim of this study was to prospectively evaluate patients with behavioral variant frontotemporal dementia (bvFTD) in a standardized manner by quantifying the degree of OC behaviors, and then use VBM to identify structural correlates. Our hypothesis was that atrophy in orbitofrontal subcortical circuits would be identified as the orbitofrontal cortex is a vulnerable structure early in bvFTD (9) and this circuit is frequently implicated in OCD.

Methods

Subjects

Patients with a diagnosis of bvFTD meeting consensus criteria (10) who presented to the Alzheimer's Disease Research Center (ADRC) at the Mayo Clinic in Rochester, Minnesota between 2008 and 2009 were recruited. Those who were unable to undergo MRI scanning or who had an MRI scan performed longer than one year prior to recruitment were not included. Patients with primary progressive aphasia were excluded. None of the patients had a pre-morbid history of obsessive-compulsive disorder (OCD) and none currently qualified for an OCD diagnosis by DSM-IV criteria (11). The patients' caregivers gave informed written consent to participate according to Mayo institutional review board (IRB) procedure. The patients' age at assessment, age at disease onset, and sex were recorded, as well as the presence of extra-pyramidal features, motor neuron disease, psychotic symptoms (hallucinations or delusions, including paranoia), stereotypies, aphasia, and genetic mutation, if known. The patients' caregivers were given the Yale-Brown Obsessive-Compulsive scale (YBOCS), a validated instrument that asks the patient to rate their obsessions and compulsions to obtain a composite score reflecting disease severity (12). The YBOCS was administered to the caregiver, rather than the patient, due to significant loss of insight that occurs in bvFTD. The same research assistant administered the YBOCS in all cases. Hyperoral behaviors, preference for sweet foods, stereotypies, and mental rigidity were not considered compulsive behaviors in this study since they do not fall under definitions of obsessions and compulsions in the YBOCS.

Seventeen consecutive patients were recruited and were given the YBOCS. Of these 17 patients, 11 were included in the study. Four were excluded because no MRI scan was performed within the same year as the survey. One was excluded because of a prior history

of idiopathic Parkinson's disease before developing FTD. One patient had an extensive, well-documented history of compulsive behaviors but none at the time of the YBOCS, resulting in a low composite score. This improvement reflected a response to new medications and the implementation of a new caregiver. This patient was felt to be unrepresentative and would be a potential confounder if included. Such significant treatment effects were not observed in any other patient in the study. The decision to remove this patient was made blinded to the MRI. Demographics of the 11 patients included in the study, as well as the excluded patients are shown in Table 1. There were no demographic differences between the 11 included patients and the six that were excluded.

Each of the 11 included patients was matched by age and gender to a healthy control subject identified from the Mayo Clinic ADRC database (Table 1). All controls performed within normal limits on standardized neurological and neuropsychological testing.

Image processing

All subjects underwent a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) imaging sequence at 3T. Parameters were: TR/TE/T1, 2300/3/900 ms; flip angle 8°, 26-cm field of view (FOV); 256 × 256 in-plane matrix with a phase FOV of 0.94, and slice thickness of 1.2 mm. All images underwent pre-processing correction for gradient non linearity (13) and intensity non-uniformity (14) as previously described (15).

Patterns of cerebral atrophy were assessed using the automated and unbiased technique of voxel-based morphometry (VBM) (16) using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). A number of preprocessing steps were performed as previously described (15). All images were normalized to a customized template and segmented using the customized tissue probability maps and the unified segmentation routine (17) into grey matter, white matter and CSF, followed by the HMRF clean-up step (18). All grey matter images were modulated and smoothed with a Gaussian kernel of 8 mm full-width at half maximum. In order to improve the quality of the normalization the customized template was created from a large group of 80 subjects with pathologically confirmed FTLT and 35 controls. Total intracranial volume (TIV) was calculated by propagating a template-drawn TIV mask to subject space, and then performing an erosion step to remove border voxels.

Statistical analysis

Two statistical analyses were performed within the SPM software (19) using the smoothed grey matter images: 1) Voxel-wise two-sample t-tests were used to compare regional grey matter volume between the bvFTD patients and controls, with age, gender and TIV included as covariates. We used the false discovery rate (FDR) procedure to control the expected proportion of false positive voxels at $p < 0.01$ (20). This approach is implemented in SPM5 under the assumption that so-called positive dependence among the hypothesis tests performed, rather than statistical independence among tests, tends to be reasonable in MRI analysis (21). 2) In the second voxel-wise analysis grey matter volume (Y) was regressed on total YBOCS score (X) in the bvFTD patients, in order to identify regions of grey matter volume that correlated with the total YBOCS score. Time from onset to scan was also included in this analysis as a covariate to account for differences in disease progression across patients. This analysis was masked by, or limited to, the results of analysis 1) in order to limit the statistical analysis only to those regions that showed significant grey matter loss in the bvFTD group as a whole. The regression was assessed uncorrected for multiple comparisons at a statistical threshold of $p < 0.001$ in order to minimize Type II error in this small sample, but was also assessed after correction for multiple comparisons using the FDR at a statistical threshold of $p < 0.01$.

In addition, in order to investigate the effects of the *MAPT* subjects on the YBOCS correlation, we used atlas-based parcellation using the automated anatomical labeling atlas (22) to measure the volume of the putamen in each bvFTD patient, and fit a linear regression model regressing volume (Y) versus YBOCS score (X). As a sensitivity analysis, we estimated this relationship among all patients and then also when excluding *MAPT* cases. These regressions were performed using the JMP computer software (JMP Software, version 6.0.0; SAS Institute Inc., Cary, NC, USA) with statistical significance set at $p < 0.05$.

Results

Table 2 describes the included patients and recorded OC behaviors. The average composite Yale-Brown obsession score for those included (11 patients) was 6.6 (20 maximum) and average compulsion score 8.3 (20 maximum) for an average composite score of 14.9 (40 maximum). One patient had extrapyramidal findings, one had signs of motor neuron disease, two had psychotic symptoms, 5 had stereotypies, and one had prominent aphasia. The average MMSE was 23.0. Five patients were on serotonergic medications at the time of interview, five were on anti-psychotics, and one was on mood stabilizing medications. The most common reported compulsive behaviors were checking (6 cases), hoarding (5 cases), ordering/arranging (5), repeating rituals (4), and cleaning (3).

In the entire sample (17 patients) the average obsession score was 5.8 and the average compulsion score was 7.8, for an average composite score of 13.6. Five had extrapyramidal findings, one had signs of motor neuron disease, five had psychotic symptoms, seven had stereotypies, and two had prominent aphasia.

A genetic mutation was known in five included patients. All of these were microtubule associated protein tau (*MAPT*) mutations, including one S305N, one R406W, one P301L, and two relatives with V337M. The excluded patient with a prior history of compulsive behaviors had a known S305N mutation.

The VBM results are shown in Figure 1. The bvFTD patients showed a pattern of grey matter loss predominantly involving the temporal lobes bilaterally, with some additional involvement of the orbitofrontal lobes, insula, striatum and parietal lobes (corrected for multiple comparisons using FDR at $p < 0.01$). Total YBOCS score correlated with grey matter loss in the left putamen, bilateral globus pallidus, and lateral temporal lobe, particularly the left middle and inferior temporal gyri (uncorrected at $p < 0.001$). No grey matter regions correlated with total YBOCS score after correction for multiple comparisons using the FDR. When the use of serotonergic medications was added as a co-variate the results were unchanged. Figure 2 demonstrates a linear association between putamen volume and YBOCS score across all bvFTD patients ($p = 0.03$), with patients tightly clustered around the line. It also shows that the relationship is little changed even when the *MAPT* patients are excluded ($p = 0.06$).

Discussion

We evaluated 11 bvFTD patients and measured the severity of OC behaviors on average 11 years after disease symptom onset. Nine of the 11 (82%) had OC behaviors and had a composite YBOCS score of greater than 10. The severity of compulsions reported was higher than that of obsessions. Among the 17 total subjects, 12 (71%) had a composite YBOCS of greater than 10.

The frequency of compulsive behaviors in this study was higher than expected. The frequency of these behaviors in FTD has been difficult to assess because of differing definitions of compulsions in this population. A prior study showing repetitive behaviors in

78% of pathology proven FTLT cases included simple repetitive behaviors (2). Another study that found the behaviors present in 38% of FTD patients at presentation did not, by design, include those who develop the behaviors at a later point (3). A prior study of stereotypical movements found that of 18 patients with FTD, 12 (67%) identified compulsions on a modified Yale-Brown checklist (4). This is similar to the 64% who had severe, persistent compulsions in a 1995 FTD study (23). The high frequency of compulsions in this study may affect the findings of the regression.

The regions of grey matter loss that correlated with degree of obsessive-compulsive behavior were the left putamen, bilateral globus pallidus, and the lateral temporal lobe, particularly the left middle and inferior temporal gyri. The findings in the basal ganglia may indicate the involvement of frontal subcortical circuits. Although we hypothesized that volumetric differences would be observed in a structure within one of these neural networks, our data does not point to one circuit as primarily responsible since the globus pallidus and putamen are involved in multiple circuits. These basal ganglia structures are involved in motor planning and patterns of action. Compulsions may either represent disinhibition of cognitive or motor behaviors, or they could be the result of dissociation of these behaviors from their reward value, which may be partly mediated by ventral striatal structures. Reciprocal projections from dopaminergic midbrain to ventral striatum and then to dorsal striatum could result in aberrant representation of reward value and motor action selection, respectively. Theories in obsessive-compulsive disorder (OCD) include an imbalance between direct and indirect pathways involving orbitofrontal cortex, or anxiety from inappropriate self-monitoring leading to a heightened sense of error that does not dissipate with action repetition. There is conflicting data regarding the neuronal networks that may be involved in OCD. Structural imaging studies have shown inconsistent volume differences between OCD patients and normal controls, and two meta-analyses have shown disparate results. One found an increased volume in the bilateral putamen and globus pallidus, particularly on the left, with reduced volume in the bilateral dorsal medial frontal cortex (24). The other showed decreased volume in the left anterior cingulate and bilateral orbitofrontal cortices (25). The drive to perform behaviors however is different in OCD than in bvFTD, as in the latter there is not the same associated anxiety. There is also no equivalent resistance to performing compulsions, and that attempt to resist may be the cause of some of the functional imaging findings in OCD, rather than the compulsions themselves.

While the orbitofrontal circuit has been implicated in OCD, there is prior data implicating the temporal lobe in compulsive behaviors in FTD. In one analysis of 90 patients, temporal atrophy and asymmetry of atrophy were independently associated with complex compulsive behaviors, whereas there was no relationship between simple compulsive behaviors and atrophy distribution, though there was more caudate atrophy (7). Another study found there were repetitive behaviors in both semantic dementia and bvFTD, but more compulsive behaviors in semantic dementia (8). A SPECT study in FTD showed that right frontal hypoperfusion was associated with stereotyped behaviors and left temporal hypoperfusion was associated with compulsions (6). Acquired OCD has been described in unilateral temporal lobe anomalies, left anterior temporal or bitemporal arachnoid cysts, or subcortical lesions (26).

Of the 11 patients in this series, there were five with *MAPT* mutations. This may influence the observed atrophy pattern given the small number of subjects. The overall atrophy pattern of the bvFTD patients included more temporal lobe involvement and less dramatic frontal atrophy. *MAPT* has been shown by VBM to have more grey matter loss in the medial temporal lobe, insula, and putamen than subjects without *MAPT* mutations, and to have predominant anteromedial temporal involvement compared to controls (27). There are also atrophy pattern variations among different *MAPT* mutations. Of the mutations involved in

this study, those with V337M (2 in this study) and P301L (1 in this study) have been shown to have more lateral temporal involvement and the S305N mutation (1 in this study) to have more medial temporal involvement (28). However, the findings in those studies showed bilateral patterns of atrophy and the significant correlation in this study was only on the left side. The five *MAPT* cases were among the top seven YBOCS scores, although the putamenal analyses findings suggest that the regression results are not being driven solely by the *MAPT* subjects. Not all subjects underwent genetic testing, so the significance of the *MAPT* mutations is uncertain. Future studies comparing compulsive behaviors and imaging from more patients with various mutations, or more with the same mutation, would be valuable (but challenging to obtain sufficiently large numbers).

The main limitation of this study is the small sample size, which could affect the validity of the statistical analysis and increase sensitivity to deviations from assumptions such as normality. Although it is difficult to evaluate the appropriateness of statistical assumptions on a voxel-by-voxel basis, the smoothing step performed in VBM is designed to make individual voxel values more approximately normally distributed since it replaces the intensity of each voxel with a weighted average of the surrounding voxels, hence smoothing out differences across voxels. Although Figure 2 only assesses putamen volume, there was no evidence of outliers which could influence the regression analysis results. Our cohort included two related patients and our linear regression methods did not account for possible within-family correlations. However, a graphical inspection of z scores for multiple regions across the brain showed that the z scores for these patients were very different and did not cluster together with respect to the other study patients. With little evidence of within-family correlation in these regions, we therefore felt that the assumption of independence among subjects was reasonable. Another limitation is that the bvFTD patients were on a variety of different medications and the effect of these medications on grey matter volume is unclear. The results did not change with adding serotonergic medications as a co-variate, but given the different medication combinations present, a medication effect cannot be excluded. The behaviors could also be influenced more by neurochemical changes rather than structural atrophy, and functional neuroimaging studies using serotonergic and other radioligands may be more fruitful.

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Figure 1.

Results of the voxel-based morphometry analyses. Top panel shows patterns of grey matter loss in the 11 bvFTD patients compared to controls. Results are shown after correction for multiple comparisons using FDR $p < 0.01$. Bottom panel shows regions of grey matter volume that correlate with YBOCS score in the bvFTD patients. Results are shown uncorrected for multiple comparisons at $p < 0.001$.

Figure 2. Correlation between total putamen volume and YBOCS score across all 11 bvFTD patients. Trend lines are shown both when the *MAPT* patients were included (solid line, $p=0.03$) and excluded (dashed line, $p=0.06$) from the analysis.

Table 1

Group demographics

	All bvFTD subjects recruited	bvFTD subjects excluded from the study	bvFTD subjects included in the study	Healthy controls*
N	17	6	11	11
% male	10 (59%)	3 (50%)	7 (64%)	7 (64%)
Age at onset, years	52.6 ± 12.7 52.0 [43-67] 30-70	54.5 ± 14.2 55 [51.3-64.8] 30-69	51.5 ± 12.4 50 [40.5-61.5] 37-70	NA
Age at evaluation/MRI, years	62.3 ± 12.1 58.0 [56-73] 42-81	61.5 ± 13.8 58 [56.5-72.3] 42-78	62.7 ± 11.8 62 [55.5-70] 44-81	62.6 ± 9.8 62 [56-70] 47-81
Onset-evaluation, years	9.7 ± 6.0 9.0 [6-12] 3-26	7.0 ± 3.6 7.5 [3.8-9] 3-12	11.2 ± 6.7 10 [6.5-14] 4-26	NA
MMSE (/30)	23.0 ± 5.6 25.0 [18-27] 13-30	23.0 ± 3.9 23.5 [21-25.5] 18-27	23.0 ± 6.5 25 [18-28] 13-30	29.2 ± 0.9 [†] 29 [28.5-30] 28-30

Data is shown as mean ± standard deviation, *median [interquartile range]*, *range*

* Each control subject was matched by age at MRI and gender to one of the 11 bvFTD patients included in the study. The gender ratios across the groups were exactly the same and the ages for each bvFTD-control pairing where matched within three years.

[†] Significant difference observed between the 11 bvFTD patients included in the study and the healthy controls at p<0.05. No significant differences were observed between the 11 bvFTD patients included in the study and the six that were excluded at p<0.05. YBOCS = Yale-Brown Obsessive-Compulsive Scale; MMSE = Mini Mental State Examination

Table 2

Characteristics of each bvFTD patient included in the study

#	Sex	Age at onset	Age at scan	YBOCS			Mutation (if known)	Description of behaviors
				Total obsession score	Total compulsion score	Total score		
1	F	37	44	11	15	26	<i>MAPT</i> S305N	"Neat freak" cleaning crumbs off table, turns lights on/off repeatedly
2	M	68	73	8	15	23		opens and closes door repeatedly, excessive washing of face and hands, turning washer/dryer on and off, looks in refrigerator repeatedly, very systematic way to make the bed
3	F	43	50	10	10	20	<i>MAPT</i> V337M	repeatedly checks locks
4	M	50	54	11	9	20	<i>MAPT</i> P301L	hoarding mail, checking things repeatedly, spends hours lining things up to be symmetrical and uniformed
5	M	56	62	6	12	18		repetitively puts on shaving lotion and shaves, hoarding of food, orderly lining up of things in cabinets and desks, goes in and out of bathroom 6 times
6	F	38	57	8	9	17	<i>MAPT</i> V337M	sexual obsessions, checks locks, opens and closes windows
7	M	38	64	11	6	17	<i>MAPT</i> R406W	hoarding junk mail, cans and bottles, checks locks repeatedly, list making
8	F	48	58	5	6	11		hoarding papers, writing everything down
9	M	67	80	3	7	10		hoards candy wrappers and paper, checks locks 10 times/day, lines up utensils and salt/pepper shakers
10	M	70	81	0	1	1		none
11	M	52	67	0	1	1		none

MAPT = Microtubule Associated Protein Tau