Neuroanatomy of Apathy and Disinhibition in Frontotemporal Lobar Degeneration

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Key Words

Neuropsychiatric inventory · Frontotemporal lobar degeneration · Apathy · Disinhibition · Magnetic resonance imaging

Abstract

Objective: To investigate the neural basis for the behavioral symptoms of frontotemporal lobar degeneration (FTLD) that cause the greatest caregiver distress. **Background:** FTLD is a progressive neurodegenerative disease associated with behavioral disturbances. Group studies have related these behaviors to volume loss on MRI. **Methods:** Forty caregivers of patients with the clinical diagnosis of FTLD completed the Neuropsychiatric Inventory. Twelve neuropsychiatric symptoms and the associated caregiver distress were assessed. Optimized voxel-based morphometry identified significant atrophy in subgroups of FTLD patients with isolated behavioral symptoms corresponding to the most distressing behaviors, and we correlated cortical atrophy directly with these distressing behavioral disorders in an unbiased group analysis. **Results:** The greatest stressors for caregivers were apathy and disinhibition ($p < 0.005$ for both contrasts). Partially distinct areas of cortical atrophy were associated with these behaviors in both individual patients with these symptoms and group-wide analyses, including

the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex in apathetic patients, and the medial orbital frontal cortex in disinhibited patients. **Conclusions:** Caregiver stress in families of FTLD patients is due in large part to apathy and disinhibition. The anatomic distribution of cortical loss corresponding to these distressing social behaviors includes partially distinct areas within the frontal lobe.

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Introduction

Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disease that affects frontal and temporal regions [1, 2]. It is the second most common form of early-onset dementia. Clinical subgroups of FTLD patients have been described, including a disorder of social comportment, personality and executive functioning (SOC/EXEC), and a progressive aphasic disturbance (APH). This study examines the neuropsychiatric symptoms most associated with caregiver distress in FTLD and investigates the neuroanatomic correlates of caregiver distress in these patients.

FTLD patients display behavioral disturbances such as apathy, disinhibition, alterations in appetite and aberrant motor behavior [3–5]. These deficits are seen in pa-

Table 1. Mean demographic and clinical features $\pm$ SD of SOC/EXEC and APH participants

	SOC/EXEC	APH	Pure disinhibition	Pure apathy	Control
Male	20	8	4	7	10
Female	6	6	1	2	17
Age, years	60.1 $\pm$ 6.9	68.5 $\pm$ 8.4	63.6 $\pm$ 9.9	63.0 $\pm$ 10.6	64.1 $\pm$ 8.6
Disease duration, months	49.2 $\pm$ 30.3	49.0 $\pm$ 27.8	55.2 $\pm$ 30.1	43.4 $\pm$ 23.4	na
Education, years	16.4 $\pm$ 3.3	15.2 $\pm$ 2.2	14.0 $\pm$ 4.0	16.9 $\pm$ 2.1	16.2 $\pm$ 2.6

There was no between-group difference with respect to disease duration and education, although SOC/EXEC patients were younger than APH patients ($t_{37} = 3.35$; $p < 0.01$).

tients with a SOC/EXEC disorder as well as APH patients [4, 6]. Studies have attempted to identify FTLD subgroups based on their behavioral profiles [4, 5, 7]. One prior study showed that agitation, disordered mood and disinhibition are very distressing to caregivers [8]. However, there is surprisingly little literature examining the neuropsychiatric symptoms that provoke distress in caregivers of FTLD patients.

Voxel-based morphometry has been used to relate neuropsychiatric symptoms to specific regions of gray-matter (GM) volume loss [6, 7, 9]. Apathy has been associated with medial frontal GM atrophy, and disinhibition with atrophy of the medial orbital frontal cortex (mOFC). In patients with so-called temporal-variant FTLD, including patients with a social disorder or semantic dementia, apathy and dietary change were the most commonly endorsed social disorders, and the total Neuropsychiatric Inventory (NPI) score correlated with dorsal medial frontal volume loss [6].

The present study sought to identify the neuropsychiatric symptoms that are most distressing for caregivers of FTLD patients. We used these caregiver stressors to guide two analyses of regional GM atrophy in FTLD patients. We examined the quantification of GM atrophy in subgroups of FTLD patients with isolated behavioral syndromes, and direct correlations of the severity of caregiver-defined behavioral disorders with GM atrophy in group-wide analyses.

Methods

Subjects

Forty patients with the clinical diagnosis of FTLD and their caregivers participated in this study. The diagnosis of FTLD was made by an experienced neurologist (M.G.) in the Department of Neurology, University of Pennsylvania School of Medicine. These

patients and their legal representatives participated in an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania.

Patients were subgrouped according to published criteria [3] that have been modified to improve reliability [10]. One subgroup of FTLD patients presented with a disorder of social comportment, personality and executive dysfunction (SOC/EXEC; $n = 26$). The second subgroup presented with a progressive form of aphasia (APH; $n = 14$). This included patients with progressive nonfluent aphasia or semantic dementia. The clinical diagnosis of a neurodegenerative disease was consistent with the results of serum studies, structural imaging studies such as MRI or CT, studies of cerebrospinal fluid (when available) and functional neuroimaging studies such as SPECT or PET, but did not involve the NPI or imaging studies used in this investigation. Exclusion criteria were, for example, the presence of other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorders such as depression or psychosis, or any systemic illness that could interfere with cognitive functioning. There was no between-group difference with respect to overall disease severity as measured by the Mini Mental State Examination [11] (mean SOC/EXEC = 21.8 ± 9.1 ; mean APH = 26.2 ± 3.1). Table 1 summarizes the demographic and clinical features of the SOC/EXEC and APH participants. Twenty-seven healthy elderly individuals served as a control group. All of these participants were living in the community and presented with no alterations in either basic or instrumental activities of daily living.

Materials and Procedures

The NPI probes 12 common neuropsychiatric symptoms and yields a measure of caregiver distress for each symptom [12]. Content validity, concurrent validity, interrater reliability and test-retest reliability of the NPI have been established by past work [12, 13]. After careful instructions, the caregivers completed the NPI. Two measures from the NPI were calculated. First, a score reflecting the total frequency and severity for each of the 12 NPI symptoms was calculated. If an abnormal behavior was present, the frequency of all individual items was rated and summed, then divided by the number of items endorsed to get the average frequency for the domain of behaviors, and then that number was multiplied by the severity rating caregivers assigned to the same domain (i.e., $F \times S$) [13]. Second, caregiver distress scores were assessed by asking the caregivers to rate their level of distress for each NPI symp-

Table 2. Mean NPI caregiver distress scores and patient severity scores $\pm$ SD

	All FTLT patients	SOC/EXEC patients	APH patients
Caregiver distress score (scale 0–5)			
Apathy	2.3 $\pm$ 1.7	3.2 $\pm$ 1.5	1.4 $\pm$ 1.5
Disinhibition	1.8 $\pm$ 1.8	2.7 $\pm$ 1.8	0.7 $\pm$ 1.2
Irritability	1.6 $\pm$ 1.6	2.3 $\pm$ 1.6	1.0 $\pm$ 1.3
Agitation	1.6 $\pm$ 1.7	2.2 $\pm$ 1.7	1.00 $\pm$ 1.4
Eating	1.4 $\pm$ 1.4	2.1 $\pm$ 1.3	0.8 $\pm$ 1.3
Depression	1.3 $\pm$ 1.6	1.4 $\pm$ 1.6	1.1 $\pm$ 1.7
Sleep	1.1 $\pm$ 1.4	1.5 $\pm$ 1.5	0.6 $\pm$ 1.3
Motor	1.1 $\pm$ 1.5	1.6 $\pm$ 1.7	0.5 $\pm$ 1.0
Anxiety	1.1 $\pm$ 1.5	1.5 $\pm$ 1.6	0.6 $\pm$ 1.1
Euphoria	0.8 $\pm$ 1.3	1.3 $\pm$ 1.4	0.3 $\pm$ 0.8
Delusions	0.7 $\pm$ 1.4	1.1 $\pm$ 1.7	0.3 $\pm$ 1.0
Hallucinations	0.3 $\pm$ 1.0	0.4 $\pm$ 1.3	0.2 $\pm$ 0.7
Patient severity score (scale 0–12)			
Apathy	4.2 $\pm$ 3.9	5.8 $\pm$ 3.8	2.5 $\pm$ 3.3
Disinhibition	2.7 $\pm$ 3.4	4.1 $\pm$ 4.0	1.1 $\pm$ 1.6
Irritability	2.3 $\pm$ 2.7	3.4 $\pm$ 3.0	1.2 $\pm$ 1.7
Agitation	2.1 $\pm$ 2.9	3.4 $\pm$ 3.3	0.7 $\pm$ 1.2
Eating	3.9 $\pm$ 3.7	5.3 $\pm$ 3.8	2.2 $\pm$ 2.7
Depression	2.0 $\pm$ 2.9	2.9 $\pm$ 3.8	1.7 $\pm$ 1.5
Sleep	2.5 $\pm$ 3.2	3.5 $\pm$ 3.5	1.4 $\pm$ 2.3
Motor	2.3 $\pm$ 3.5	3.2 $\pm$ 3.8	1.3 $\pm$ 2.9
Anxiety	1.5 $\pm$ 2.3	2.4 $\pm$ 2.8	0.6 $\pm$ 0.9
Euphoria	1.7 $\pm$ 2.9	2.7 $\pm$ 3.4	0.5 $\pm$ 1.5
Delusions	1.2 $\pm$ 2.7	1.8 $\pm$ 3.4	0.6 $\pm$ 1.7
Hallucinations	0.6 $\pm$ 2.0	1.1 $\pm$ 2.7	0.1 $\pm$ 0.3

tom using a 5-point Likert scale (i.e., 0 = not at all; 1 = minimally; 2 = mildly; 3 = moderately; 4 = severely; 5 = extremely). NPI and MRI studies were all carried out on the same day.

Imaging Data Acquisition and Analysis

We evaluated MRI in a subgroup of 32 patients (APH: $n = 14$; SOC/EXEC: $n = 18$) matched with the entire group of patients for demographic and clinical characteristics. These patients were compared to 27 healthy, demographically matched controls. High-resolution T_1 -weighted 3-dimensional spoiled gradient echo images were acquired with TR = 1,620 ms, TE = 3 ms, slice thickness = 1 mm, flip angle = 30°, matrix = 192 $\times$ 256 and in-plane resolution = 0.98 $\times$ 0.98 mm by a Siemens Echosped 3-tesla MRI scanner.

A novel symmetric diffeomorphism procedure was used to normalize high-resolution T_1 -weighted MR images for shape and intensity [14, 15], using a local template consisting of 25 healthy seniors and patients. We used high-dimensional normalization and template-based cortical segmentation to quantify GM changes. A spatially dense mapping, or correspondence, between the template and a population of experimental images was first computed. The brain image was modeled as a dense continuum, sampled at individual voxels, that was accompanied by a transformation model that preserved neighborhood relationships among vox-

els even under very large deformations. This strategy enabled a high-resolution, smoothly flowing deformation of these voxels into the corresponding voxels of the template that was able to capture both large-scale atrophy and subtle, focal disease effects. Moreover, the mapping process with the template used a bidirectional algorithm to build maps from the set of experimental brains into a template and simultaneously from the template into the population of experimental brains. We also used these methods to estimate an unbiased local template composed of the controls and patients participating in these studies. This approach allowed us to perform statistical contrasts between groups at a high spatial resolution and with less smoothing, because both neighboring voxels and large-scale features are maintained, while at the same time there is reduced variance in the estimated location of the neuroanatomy. The resulting images were then segmented using FMRIB's Automated Segmentation Tool [16], which labeled the brain volumes into GM, white matter, CSF and 'other' with inhomogeneity correction. GM images were then multiplied by the logarithm of their corresponding Jacobian registrations to template space, which resulted in normalized, spatially varying estimates of GM volume for each subject [14]. GM images were subsampled to 2 mm $\times$ 2 mm voxel sizes, and then warped into Montreal Neurologic Institute space using the log-Jacobians of the Montreal Neurologic Institute space-warped template. Images were smoothed with an 8-mm full width at half maximum Gaussian filter, and contrasted with a cohort of 27 age-matched controls using an independent-sample t test, as described elsewhere [17]. The analysis included all voxels containing any GM in the volume, thus resulting in a true whole-brain analysis. Implicit masking (i.e., use of a dummy value to exclude voxels with a value of 0) was used to ignore zeros, and global calculation was omitted.

Two analyses were performed to associate caregiver distress with regional GM atrophy. In the first analysis, we identified significant GM atrophy in the subgroups of patients with isolated behavioral syndromes composed of the most distressing behaviors, relative to healthy seniors. We accepted as significant a cluster with a volume of 100 adjacent voxels and a voxel height threshold of Z score >3.09 (equivalent to $p < 0.001$). In the second analysis, we used the regression module of Statistical Parametric Mapping 2 to relate GM atrophy in the entire FTLT population directly to the specific behavioral disorders that are most distressing. We used the findings of the atrophy analysis to mask the regressions. In this manner, we were able to restrict our interpretation of the regression analysis to those brain regions known to be significantly atrophic and highly likely to have disease. The statistical threshold for the regression analyses was set at $p < 0.01$, following correction for multiple comparisons with a false discovery rate for both voxel level and cluster level analyses, and we accepted only clusters comprised of 40 or more adjacent voxels.

Results

Total NPI Scores

The frequency/severity scores for all 12 NPI symptoms and their corresponding caregiver distress scores are summarized in table 2. The mean $\pm$ standard deviation (SD) for F $\times$ S values for all 12 NPI symptoms was 2.00

± 1.99 . To determine whether a symptom reflected significant disease severity, we used a cutoff of 3.99 or a value of 1 SD above the mean. Because NPI data were not normally distributed, nonparametric statistical tests such as Mann-Whitney U and Spearman were used. The total $F \times S$ NPI score was elevated in SOC/EXEC patients compared to APH patients ($U = 44.5$; $p = 0.001$). Caregivers of SOC/EXEC patients reported higher levels of distress compared to caregivers of APH patients ($U = 89.5$; $p = 0.003$).

Individual NPI Symptoms

Caregiver distress was not equally distributed across all 12 NPI symptoms. As summarized in table 2, symptoms yielding the greatest distress for all FTLN caregivers were apathy and disinhibition. Apathy also provided the greatest distress for caregivers of both SOC/EXEC and APH subgroups. Higher caregiver distress scores were found for both of these symptoms for SOC/EXEC caregivers compared to APH caregivers (apathy: $U = 80.0$; $p = 0.002$; disinhibition: $U = 77.5$; $p = 0.001$). Irritability ($U = 89.5$; $p = 0.010$), agitation ($U = 99.5$; $p = 0.021$) and disordered eating ($U = 89.0$; $p = 0.006$) also proved distressing, with SOC/EXEC caregivers rating these symptoms more distressful than APH caregivers.

Caregiver distress scores and $F \times S$ severity scores were highly correlated, suggesting that caregiver distress reflected the behavioral disturbance of FTLN patients. Overall, caregiver distress correlated with the severity of the social disorder in FTLN ($s = 0.84$; $p < 0.001$). This was true for both the SOC/EXEC ($s = 0.77$; $p < 0.001$) and the APH ($s = 0.82$; $p < 0.001$) subgroups. Caregiver distress reflected the severity of the behavioral disturbance for both of the most distressing behaviors – apathy (SOC/EXEC: $s = 0.81$; $p < 0.001$; APH: $s = 0.79$; $p < 0.001$) and disinhibition (SOC/EXEC: $s = 0.76$; $p < 0.001$; APH: $s = 0.86$; $p < 0.001$).

Imaging Analysis

In the first analysis, we identified subgroups of patients with a social and behavioral abnormality exclusively involving apathy, or disinhibition, using the criterion of a severity ($F \times S$) score ≥ 4 in only one social domain. The clinical and demographic characteristics of these patient subgroups are provided in table 1. In the purely apathetic group ($n = 8$), we found a mean $\pm$ SD $F \times S$ score of 7.2 ± 2.7 for apathy but one of 2.7 ± 3.3 for disinhibition. In the purely disinhibited group ($n = 4$), a mean $\pm$ SD $F \times S$ score of 6.3 ± 3.6 was found for disinhibition and one of 2.0 ± 2.7 for apathy.

Table 3. Cortical atrophy in patients with specific behavioral syndromes

Anatomic locus	Coordinates			Z score
	x	y	z	
Apathetic patients (n = 8)				
Bilateral medial frontal (32/24)	-2	41	9	4.94
L. orbital frontal (47)	-14	21	-16	4.97
L. inferior frontal (45)	-36	25	4	5.14
L. dorsolateral prefrontal (46)	-46	26	23	5.12
L. polar frontal (10)	-10	51	1	4.98
L. ventral medial frontal (11)	-2	40	-12	4.94
L. medial frontal (11/25)	-26	34	-12	5.67
L. insula	-36	10	9	5.35
L. caudate	-16	10	14	5.10
L. uncus (28)	-24	2	-29	4.80
L. parahippocampal (36)	-36	-26	-22	5.02
L. superior temporal (39)	-51	-63	27	3.74
R. orbital frontal (11)	10	26	-18	4.93
R. ventral medial frontal (11)	18	48	-19	4.84
R. inferior frontal (44)	36	13	23	5.19
R. dorsolateral prefrontal (46)	50	30	24	3.97
R. premotor (6/8)	6	24	43	4.96
R. middle temporal (21/20)	53	-18	-18	5.60
R. insula	50	-34	22	3.26
R. amygdala	22	-9	-15	5.32
R. caudate	32	12	7	5.07
R. inferior parietal (40)	51	-42	48	4.28
Disinhibited patients (n = 4)				
L. orbital frontal (11)	-10	16	-20	5.63
L. inferior frontal (45)	-48	26	19	3.49
L. insula	-44	22	8	4.17
L. medial frontal (25)	-12	14	-14	4.33
L. inferior frontal (47)	-26	22	-18	4.19
L. polar frontal (10)	-26	54	-9	4.11
L. medial frontal (10)	-14	44	12	4.34
L. prefrontal (9)	-28	35	35	3.74
L. precentral (8)	-10	47	38	3.63
L. premotor (6)	-57	0	42	3.23
L. middle temporal (21/20)	-67	-20	-17	4.09
L. amygdala/uncus	-26	-4	-24	4.25
L. medial temporal	-36	-22	-12	3.98
L. superior parietal (7)	-16	-65	62	3.77
L. occipital (19)	-26	-57	-12	4.54
R. orbital frontal (11)	10	40	-20	4.20
R. inferior frontal (45/10)	46	16	4	3.85
R. temporal (21/39)	55	-46	13	3.12
R. insula	36	8	10	4.21
R. inferior frontal (47)	50	40	-10	4.17
R. ventral medial frontal (11)	6	56	-22	4.22
R. precentral (44)	52	6	8	4.37
R. middle frontal (46)	50	30	28	4.38
R. occipital (19)	22	-59	-12	3.80

The corresponding Brodman area is indicated by the figure in parentheses. L. = Left; R. = right.

Fig. 1. Anatomic distribution of significant cortical atrophy in patients with relatively exclusive disorders of apathy (A) or disinhibition (B).

Fig. 2. Significant correlations of cortical atrophy with apathy (A) and disinhibition (B) scores.

We contrasted GM atrophy in these socially impaired subgroups compared to controls. These areas are summarized in table 3 and illustrated in figure 1. Significant GM atrophy for patients showing only an abnormality of apathy was evident in the medial frontal region bilaterally, including the dorsal anterior cingulate cortex and mOFC, and bilateral inferior frontal, bilateral ante-

rior temporal, and right dorsolateral prefrontal cortex (dlPFC) regions. Patients showing only an abnormality of disinhibition demonstrated significant GM atrophy in the mOFC, bilateral inferior frontal, bilateral anterior temporal and left dlPFC regions.

The atrophy-masked correlations of GM loss significantly associated with disinhibition and apathy scores are

Table 4. Masked correlations of cortical atrophy significantly associated with apathy and disinhibition

Anatomic locus	Coordinates			Z score
	x	y	z	
Apathy				
Bilateral medial frontal (32/24)	4	46	27	4.90
Bilateral caudate	10	18	3	3.82
L. inferior frontal (45/47)	-42	23	-8	4.69
L. dorsolateral prefrontal (46/9)	-50	28	19	3.83
L. polar frontal (10)	-26	54	-4	3.52
R. orbital frontal (11/25)	22	20	-18	4.47
R. inferior frontal (44)	48	31	8	4.19
R. dorsolateral prefrontal (46)	50	23	28	4.01
R. premotor area (6/8)	28	8	49	4.05
R. middle temporal (21)	53	-20	-7	3.80
Disinhibition				
L. orbital frontal (11/47)	-44	22	6	3.23
L. inferior frontal (45)	-55	29	0	3.17
L. insula	-30	15	-16	3.15
R. orbital frontal (25/11)	12	15	-16	3.11
R. inferior frontal (45)	34	18	6	3.11
R. middle temporal (21)	53	-26	-8	3.88
R. insula	50	8	-1	3.18

The corresponding Brodman area is indicated by the figure in parentheses. L. = Left; R. = right.

illustrated in figure 2, and the location of peak voxels within each of these significantly atrophic clusters is summarized in table 4. For apathetic behavior, bilateral medial, orbital, inferior and dorsolateral frontal areas showed significant GM loss correlating with $F \times S$ apathy ratings. Right middle temporal and right caudate regions were also highly correlated with this behavior. For disinhibited behavior, GM areas found to be significantly associated with $F \times S$ ratings were bilateral orbital and inferior frontal, bilateral insula and right middle temporal regions.

Discussion

Caregivers are significantly distressed by the social behaviors of patients with FTLT. This includes both the subgroup of SOC/EXEC patients with obvious social deficits and APH patients who have subtler social impairments. Caregivers of SOC/EXEC patients have significantly higher distress levels than APH caregivers. The most distressful behavior for both SOC/EXEC and APH patients was apathy, although disinhibition was also very

distressing. Caregiver distress was highly correlated with symptom frequency and severity in FTLT, indicating that caregiver distress accurately reflected social disorders in these patients.

Abnormal social behaviors are well recognized in FTLT [4, 5, 7, 18–20]. We found apathy to be the most frequently observed symptom, consistent with prior work [4–7, 9]. Disinhibition is noted almost as often [7, 9]. Like other investigators, we found distressful symptoms such as apathy and disinhibition to be evident in both the SOC/EXEC and APH groups [4, 6]. However, somewhat different social changes were seen in SOC/EXEC and APH subgroups [4]. We observed abnormal eating-related behaviors to be fairly frequent, also described by others [4, 6, 7, 9].

While the precise basis for a social disorder continues to be an active area of investigation, its profound consequences on a wide variety of daily activities are clear [21]. In this context, it is unfortunate that there have been so few studies investigating caregiver distress in FTLT. One prior study used the Frontal Behavioral Inventory to investigate the social disorder in FTLT [22]. These investigators reported that disinhibition and executive dysfunction are predictive of caregiver burden [23]. Others examined the correlation between abnormal behaviors and distress. Unlike our results, they found the most distressing behaviors to be agitation/psychosis and a mood disorder [8]. Disinhibition was only mildly related to caregiver distress, and apathy was not significantly related to distress. These results may have differed from ours because the investigators examined clusters of behavior rather than specific behaviors individually.

Our study used a novel, symmetric diffeomorphism method of image analysis to investigate GM atrophy. The transformation model took into account both whole-brain and local-neighborhood relationships to optimize the identification of GM atrophy. Moreover, this was performed in an unbiased manner that related these brains to the template in a bidirectional manner, thereby avoiding the potential confound associated with traditional, unidirectional mapping that is biased by the nature of the template. The symmetry achieved in this optimization significantly improves normalization compared to unidirectional template mapping [24]. These types of high-dimensional, unbiased maps also benefited normalization accuracy because of the reduced variance in the probable location of a structure following deformation. With this approach, we had the advantage of being able to perform statistical contrasts between groups at a higher spatial resolution, with less smoothing and with great-

er statistical confidence, than was previously achieved with parametric or elastic methods. Parametric and elastic methods are limited because they cannot guarantee that neighboring voxels are maintained, while at the same time capturing highly deforming transformations that align both the large-scale features as well as the local topography of the brain. The statistical superiority of symmetric diffeomorphisms, relative to available parametric and elastic methods, has been demonstrated experimentally in the propagation of neuroanatomic labels across a population of elderly and neurodegenerative brains [15] and in localizing activation in small brain structures such as the hippocampus [25].

With this imaging approach, we found partially distinct patterns of cortical atrophy in subgroups of patients with relatively exclusive apathy or disinhibition syndromes. Significant GM loss associated with both behaviors occurred in the bilateral mOFC, bilateral inferior frontal and bilateral anterior temporal regions. We also observed relatively distinct anatomic distributions of atrophy associated with each behavioral disorder. Apathy was associated with atrophy in the dorsal anterior cingulate cortex and right dlPFC, while disinhibition was associated with left dlPFC atrophy. Lesion studies also have demonstrated distinct anatomic substrates for these behavioral impairments, associating the dorsal anterior cingulate cortex with apathy and impaired initiation [26], and lesions of the ventral frontal region with disinhibition [27, 28]. We found mOFC disease in both disinhibited and apathetic subgroups. One possible account may be related to the anatomic extent of atrophy that is greater in the apathetic subgroup than the disinhibited subgroup. Clinically, we have observed that patients who are disinhibited can become apathetic over time. From this perspective, GM disease may expand longitudinally in FTLT by spreading from the OFC, associated with disinhibition, to involve the anterior cingulate cortex, associated with apathy. We tested this hypothesis by examining the average disease duration of apathetic and disinhibited subgroups to see if disinhibition regularly precedes apathy. However, these two subgroups did not differ in their disease durations. This hypothesis cannot be tested adequately in a cross-sectional sample. Longitudinal studies will be needed to examine this hypothesis more rigorously. Alternate hypotheses are that different histopathologic abnormalities or distinct white matter changes underlie these phenotypes, although this remains to be investigated.

Although the dlPFC is generally not associated with behavioral disturbances, we observed GM loss in this area in our apathetic cohort. Functional MRI studies im-

plicate the dlPFC in attentional and organizational aspects of social functioning [29, 30]. Patients may appear apathetic if they have difficulty developing an independent plan to initiate an activity, for example, and instead are dependent on their caregivers for planning and organizing an activity. This is consistent with the hypothesis that impoverished organizational abilities will result in the appearance of apathy in patients with FTLT.

While we are not aware of prior attempts to identify subgroups of FTLT patients who exhibit specific behavioral disorders, several studies have used correlational techniques to demonstrate the association between particular brain regions and specific behaviors in FTLT. In one study, apathy was associated with rostral medial prefrontal atrophy, and disinhibition correlated with subgenual prefrontal atrophy [9]. Not all studies have demonstrated distinct anatomic associates of abnormal behaviors. Patients with frontal cortical atrophy showed apathy, anxiety and eating disorders, while patients with temporal cortical atrophy showed sleep disturbances [7]. However, both FTLT subgroups showed greater ventral medial prefrontal atrophy than patients with Alzheimer's disease. A PET study reported a correlation between disinhibition scores on the NPI and OFC activity in FTLT, while patients with impaired apathy also revealed greater OFC involvement than those without apathy [31]. Patients with an eating disorder have atrophy in OFC and insula regions [32, 33]. Observations such as these raise questions about the role of OFC in disinhibited behavior. Several prior studies of FTLT emphasized the right-lateralized disease of patients with a social disorder [7, 9, 32, 34, 35]. Right-lateralizing findings can also be seen in apathetic patients with structural disease [28]. The correlation study in the present report showed bilateral involvement, as reported in other work [33, 36, 37]. This may have been due in part to the inclusion of patients with SOC/EXEC phenotype and an APH phenotype. However, this would not explain the imaging findings in the FTLT patients with specific disorders of social functioning who did not demonstrate strongly lateralized atrophy. One possibility is that our diffeomorphic imaging technique supported statistical analyses with smaller voxels, thereby allowing finer grained assessments of GM atrophy. Additional work is needed to examine FTLT patients displaying specific behaviors.

Recent research [9] reported a relationship between apathy and disinhibition as measured with the NPI and atrophy involving the right medial superior frontal gyrus and right subgenual cingulate gyrus, respectively. These data complement the results in our study [6, 7, 9]. Unlike

the prior research [9], we used the NPI indices of caregiver distress to guide our analysis. Also, prior research [9] used a region of interest image analysis identifying a priori regions of interest corresponding to specific anatomic distributions and a statistical correction for small volumes in order to achieve statistical significance. In the current study, whole-brain analysis was used that is not biased by a priori expectations, and statistical significance was obtained in the critical cortical areas without a small volume correction. This is important because constructs such as apathy are complex and multifactorial, and a whole-brain analysis is important for determining the additional neural substrates that may be contributing to these disorders. Moreover, the present study is unique because we identified individual patients with a relatively selective disorder of apathy or disinhibition, i.e., patients with minimal behavioral abnormalities in other domains. In these unique cohorts of patients, we found cortical atrophy relative to healthy seniors that largely corresponds to the group-wide correlative analysis of social disorders. This provides converging evidence from a different approach that is needed to support previous correlative studies. It would be valuable to associate these behavioral syndromes with specific pathogenic proteins implicated in FTLT, such as 3-repeat and 4-repeat tau and various subtypes of TDP-43.

Although the NPI is thought to be a valid and reliable tool, it is nevertheless a subjective measure of behavioral symptoms, and observer bias may therefore be present. Also, the NPI was not originally designed to be used with FTLT patients. This may suggest some limitations on the external validity of our findings. Additional studies of behavioral disorders are required using instruments that are less susceptible to bias. Only a small number of patients displayed a relatively isolated behavioral deficit. The NPI may not be discrete enough to identify isolated behavioral syndromes. Experimental studies examining the basis for a social disorder would be useful in explaining the mechanisms underlying these distressing conditions [32, 38]. With these caveats in mind, we conclude that neuropsychiatric symptoms in FTLT are quite distressing for caregivers, and these clinical features are associated with partially distinct anatomic distributions of frontal atrophy.

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