Apathy and disinhibition in frontotemporal dementia

Insights into their neural correlates

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ABSTRACT

Background: Aberrant social behavior is a defining symptom of frontotemporal dementia (FTD) and may eventually occur in all syndromes composing the FTD spectrum. Two main behavioral abnormalities have been described: apathy and disinhibition, but their neuroanatomical correlates remain underspecified.

Methods: Sixty-two patients with a clinical diagnosis of FTD participated in the study. Voxel-based morphometry of MRI data was performed to explore the association between gray matter loss and severity of the two behavioral profiles as measured by the Apathy and Disinhibition subscales of the Frontal Systems Behavior Scale.

Results: Compared with a group of controls, the FTD group showed extensive bilateral atrophy predominantly involving frontal and temporal lobes. Within the FTD group, the severity of apathy correlated with atrophy in the right dorsolateral prefrontal cortex. The severity of disinhibition correlated with atrophy in the right nucleus accumbens, right superior temporal sulcus, and right mediotemporal limbic structures.

Conclusions: Prefrontal and temporal regions are differentially associated with apathy and disinhibition. Our results support the view that successful execution of complex social behaviors relies on the integration of social knowledge and executive functions, represented in the prefrontal cortex, and reward attribution and emotional processing, represented in mesolimbic structures.

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GLOSSARY

ACC = anterior cingulate cortex; **BA** = Brodmann area; **DLPFC** = dorsolateral prefrontal cortex; **FrSBe** = Frontal Systems Behavior Scale; **FTD** = frontotemporal dementia; **FWE** = family-wise error; **Mattis-DRS** = Mattis Dementia Rating Scale; **NPI** = Neuropsychiatric Inventory; **NS** = not significant; **OFC** = orbitofrontal cortex; **VBM** = voxel-based morphometry.

The notion that specific brain structures in humans are specialized for complex social behaviors has received extensive support in cognitive neuroscience.¹ Several studies of patients with focal brain lesions and socially inappropriate behaviors have demonstrated the central role of the prefrontal cortex in social behaviors.²⁻⁴ In addition, many authors have focused on the functional importance of frontosubcortical circuits in determining behavioral abnormalities, given the extensive interconnection between basal ganglia and the prefrontal cortex.^{5,6} With the advent of brain imaging, other brain structures, primarily known from animal studies to be involved in emotion perception and reward processing (i.e., amygdala and striatum), have been identified as having a fundamental role in complex social behaviors such as cooperation and donation.⁷⁻⁹ Therefore, there is evidence that a complex brain network involving frontal, subcortical, and mesolimbic structures mediates social behavior, but how each brain region contributes to different behavioral abnormalities remains unclear. In particular, the specific contributions of the temporal lobes and subcortical structures need to be clarified.

Supplemental data at
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Inappropriate social behavior is a defining symptom of frontotemporal dementia (FTD),^{10,11} which embraces a spectrum of different clinical syndromes, mainly distinguished on the basis of whether the presentation is primarily behavioral or aphasic. Behavioral abnormalities can eventually occur in all the FTD syndromes, although they are predominant in the behavioral variant.¹⁰ Therefore, FTD offers essential insights to understand the neural correlates of social behavior, and correlations between volume loss in particular brain structures and specific behavioral abnormalities in FTD have been recently established.^{12,13} In FTD, two distinct behavioral profiles have been reported.^{14,15} Some patients predominantly present with apathy, inertia, and loss of volition. Usually the presence of the caregiver is necessary to push them to initiate even simple tasks. Others patients predominantly present with impulsiveness, disinhibition, and hyperactivity. They may show excessive jocularity, undue familiarity, irritability, and sexual acting out. The two profiles have been termed as “apathetic” and “disinhibited.” The distinction is evident especially in the early stage of the disease, whereas in later stages they may overlap.¹⁵

Despite the general importance of behavioral symptoms in FTD, few studies have specifically focused on the neural correlates of the apathetic and disinhibited profiles.^{14,16,17} Patients were usually divided in two groups based on the clinical judgment of examiners or on single sub-items of the Neuropsychiatric Inventory (NPI).¹⁸ But the comparison between groups does not take into account the overlap between the two behavioral abnormalities that may occur as atrophy expands. No correlation studies investigating the association between the degree of gray matter loss and more comprehensive measures of apathy and disinhibition in FTD have been conducted so far.

In the present study, we used voxel-based morphometry (VBM) of MRI data to assess gray matter changes associated with apathy and disinhibition in a group of 62 FTD patients. VBM has been successfully and reliably used to determine correlations between atro-

phy in specific areas and symptoms in patients with FTD^{12,13} and other types of dementia.¹⁹

To measure behavioral symptom severity, we adopted a questionnaire where sub-items representing several behavioral disturbances are aggregated into scores for apathy and disinhibition (Frontal Systems Behavior Scale [FrSBe]).²⁰ We hypothesized that not only prefrontal cortex but also subcortical and limbic regions would show a differential role in determining apathy and disinhibition, according to evidence from cognitive neuroscience demonstrating the role of structures such as striatum and amygdala in complex social behaviors.¹

METHODS Subjects. Sixty-two patients with clinically diagnosed FTD participated in the study. They were referred by outside providers to the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke and enrolled in an ongoing study to further characterize patients with FTD. Written informed consent for the study, which was approved by the National Institute of Neurological Disorders and Stroke Institutional Review Board, was obtained from a family member. Assent from the patient was required in all circumstances and at all times. During a single 1-week visit at the NIH, patients received extensive clinical and neuropsychological evaluations and underwent brain MRI. The diagnosis was confirmed according to published criteria.¹¹ Forty-eight patients were characterized clinically as having FTD with prominent behavioral disturbances (behavioral presentation), whereas the remaining 14 patients had a clinical syndrome characterized by early changes in language function (aphasic presentation).

For the imaging study, 14 age-matched healthy controls underwent an MRI in the same scanner used for patients. They gave informed consent and were paid for their participation. Patients' and controls' characteristics are reported in table 1.

Behavioral assessment. Frequencies and characteristics of behavioral disturbances were assessed using the FrSBe,²⁰ a questionnaire designed to provide a measure of behavior before and after a damage or illness occurs. It is completed by the patient in a self-assessment and by the patient's caregiver, who have to rate the frequency of 46 different behaviors on 5-point Likert scales. The 46 items are structured in three theoretically derived^{5,6} subscales that measure three frontal syndromes: Apathy (subscale A), Disinhibition (subscale D), and Executive Dysfunction (subscale E). Among the available questionnaires measuring behavioral disturbances, the FrSBe is particularly useful in characterizing the two behavioral FTD profiles, because it gathers several complex behaviors in synthetic subscales (namely, A and D). As an example, behaviors such as “sits around doing nothing” and “has difficulty starting an activity, lack initiative” are summarized in subscale A, which corresponds to the apathetic profile. Behaviors such as “can't sit still, is hyperactive” and “does risky things” are summarized in subscale D, which represents the disinhibited profile.

Imaging. A 1.5-tesla GE MRI scanner (GE Medical Systems, Milwaukee, WI) and standard quadrature head coil were used to obtain all images. A T1-weighted spoiled gradient echo sequence

Table 1 Characteristics of patients and healthy controls

Group	n	Sex, M:F	Age, mean $\pm$ SE	Years of education, mean $\pm$ SE	FrSBe total score, mean $\pm$ SE	FrSBe apathy, mean $\pm$ SE	FrSBe disinhibition, mean $\pm$ SE	FrSBe executive function, mean $\pm$ SE
Control	14	7:7	60.6 $\pm$ 1.7	17.2 $\pm$ 1.0	—	—	—	—
FTD	62	29:33	61.2 $\pm$ 1.0	15.5 $\pm$ 0.4	98.1 $\pm$ 2.9	95.6 $\pm$ 3.3	80.3 $\pm$ 3.1	93.6 $\pm$ 2.6
Behavioral FTD	48	21:27	60.2 $\pm$ 1.1	15.4 $\pm$ 0.4	101.9 $\pm$ 2.7	98.6 $\pm$ 3.5	84.2 $\pm$ 3.4	97.2 $\pm$ 2.5
Aphasic FTD	14	8:6	63.0 $\pm$ 2.3	15.9 $\pm$ 0.5	85.0 $\pm$ 8.0	85.3 $\pm$ 8.6	66.9 $\pm$ 5.8	82.3 $\pm$ 7.1

Frontal Systems Behavior Scale (FrSBe) T scores are derived from the caregiver form, referring to the present time. FTD = frontotemporal dementia.

was used to generate 124 contiguous 1.5-mm-thick axial slices (repetition time = 6.1 msec; echo time = min full; flip angle = 20°; field of view = 240 mm; 124 slices, slice thickness = 1.5 mm; matrix size = 256 $\times$ 256 $\times$ 124).

Voxel-based morphometry: Processing and analysis.

VBM analysis of the data were performed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) using a unified segmentation algorithm.²¹ The segmented and modulated normalized gray matter images were smoothed with a 12-mm full-width at half-maximum filter.

To provide an overall indicator of gray matter atrophy distribution in the FTD patients, a two-sample comparison between patients and controls was performed, including age, sex, and total intracranial volume as confounding covariates. In this analysis, the voxel level statistical threshold was set at $p < 0.05$ corrected for multiple comparisons. Family-wise error (FWE) correction, which computes a correction for all voxels controlling for the chance of any false positives, was adopted as the most stringent correction for multiple comparisons available in SPM.²² Subsequently, to identify gray matter changes correlated with the severity and pattern of behavioral abnormalities, a covariate-only analysis was performed within the FTD group. Standardized T scores²³ of FrSBe subscales A and D (caregiver form referring to the present time) were entered as regressors into the model with age, sex, total intracranial volume, and dementia severity (Mattis Dementia Rating Scale age- and education-matched scaled score [Mattis-DRS]) as confounding covariates. FrSBe subscale E was not entered into the model because it was highly correlated with subscales A and D (Pearson $r_{62} \geq 0.7$; for a discussion of the fallacies of including highly correlated variables as predictors in multiple regression models, see reference 24). The relationship between voxel values and the behavioral profile of interest was examined using one-tailed t tests, assuming that increasing severity of the behavioral score would be associated with decreased tissue density. In addition, we also tested whether there were regions surviving a corrected threshold in which increased atrophy would be associated with better behavioral scores.

Whole-brain correlational analyses were performed setting the voxel-level uncorrected statistical threshold at $p < 0.001$, with an additional cluster extent threshold of 30 voxels. Whole-brain FWE correction ($p < 0.05$) was also applied. Uncorrected findings are discussed only if located in frontal, temporal, or subcortical structures known to be important in social behavior for which we had predictions.

SPSS (15.0 for PC) was used to analyze the correlation between FrSBe subscales and demographical and behavioral variables included in the model and to carry out statistical comparisons between diagnostic subgroups. In addition, after the VBM analysis, gray matter density peak values of the identi-

fied regions were extracted and entered in multiple regression analyses performed in SPSS. This allowed us to measure how significantly the gray matter density of the identified regions predicted the FrSBe subscales' scores. Patients' gray matter density peak values of all the resulting regions and the variables included into the SPM model were entered as predictors in stepwise regression analyses in which the dependent variables were the corresponding FrSBe subscales.

RESULTS Clinical characteristics of the FTD group.

The average total standardized (T) FrSBe score (mean score $\pm$ SE = 98.1 $\pm$ 2.9, with a score of 65 as the threshold of clinical significance) was elevated in the entire patient group, as well as in both the behavioral and aphasic FTD subgroups (table 1), showing that behavioral abnormalities do occur also in the aphasic FTD clinical syndrome. Independent t tests showed that there were no significant differences between the two diagnostic subgroups on the FrSBe Total, Apathy, and Executive Function scores ($t_s < 2$, $df = 60$, not significant [NS]), whereas the behavioral FTD group was more impaired than the aphasic FTD group on the FrSBe Disinhibition score ($t = 2.42$, $df = 60$, $p = 0.019$). The two subgroups did not significantly differ in demographical characteristics such as age, education, and disease duration ($t_s < 1$, $df = 60$, NS).

Among all patients, the FrSBe Apathy subscale was correlated with the Disinhibition subscale (Pearson $r_{62} = 0.44$, $p < 0.01$), demonstrating that the two behavioral profiles overlap at the time of assessment. Neither the Apathy nor the Disinhibition subscale was significantly correlated with disease duration measured in years since symptoms' onset and months since diagnosis (Pearson $r_{s62} < 0.2$, NS). The FrSBe Executive Dysfunction subscale was highly correlated with both Apathy (Pearson $r_{62} = 0.71$, $p < 0.0005$) and Disinhibition (Pearson $r_{62} = 0.70$, $p < 0.0005$). No significant correlations were found between each FrSBe subscale and any of the other variables included in the SPM model (sex, age, Mattis-DRS, and intracranial volume).

VBM results. Compared with healthy controls, the FTD group showed widespread bilateral atrophy pre-

Table 2 Regions of gray matter loss associated with the apathetic and disinhibited profiles

Region	Anatomical localization	Side	Cluster size	x	y	z	Peak Z value
FrSBe subscale A (apathetic profile)							
Dorsolateral prefrontal cortex	Inferior frontal gyrus, BA 45	R	248	51	22	17	4.80*
	Middle frontal gyrus, BA 10	R	34	34	57	12	3.62
	Middle frontal gyrus, BA 9	L	106	-34	42	33	3.97
	Superior frontal gyrus, BA 8	L	44	-34	20	49	3.66
	Inferior frontal gyrus, BA 45	L	44	-46	18	19	3.57
	Middle frontal gyrus, BA 46	L	43	-44	32	15	3.57
Lateral orbitofrontal cortex	Middle frontal gyrus, BA 10/11	R	76	40	48	-16	3.81
	Inferior frontal gyrus, BA 47	R	103	51	37	-2	3.75
Medial prefrontal cortex	Rostral anterior cingulate, BA 32	R	30	8	45	7	3.55
	Caudal anterior cingulate, BA 32	R	32	12	6	40	3.56
Striatum	Putamen	R	33	24	12	-1	3.27
Temporoparietal junction	Inferior parietal lobulus, BA 40	R	31	65	-28	31	3.59
FrSBe subscale D (disinhibited profile)							
Limbic lobe	Amygdala, hippocampus, uncus, BA 34/28/35	R	1,025	36	-17	-21	4.71**
Lateral temporal lobe	Middle temporal gyrus, BA 37	R	57	51	-56	3	3.93*
	Middle temporal gyrus, BA 21	R	103	55	-16	-18	3.85*
Striatum	Nucleus accumbens	R	35	10	17	-8	3.75*

All regions exceed an uncorrected statistical threshold of $p < 0.001$ (minimum cluster size 30 voxels). Coordinates are in Talairach space.

*Regions surviving the most stringent whole-brain correction for multiple comparisons (family-wise error) at $p < 0.05$.

**Regions surviving the whole-brain false-discovery rate-corrected threshold at $p < 0.06$.

FrSBe = Frontal Systems Behavior Scale; BA = Brodmann area.

dominantly involving mediofrontal and orbitofrontal regions, anteromedial temporal areas, insula, and basal ganglia ($p_{\text{FWE-corrected}} < 0.05$; see table e-1 and figure e-1 on the *Neurology*[®] Web site at www.neurology.org). The distribution of atrophy in FTD patients is consistent with previous VBM studies of FTD.^{12,13,25}

Several distinct regions, mainly localized in the right hemisphere, showed a significant correlation between gray matter loss and increased severity of FrSBe scores for apathy and disinhibition. At the corrected threshold, no regions showing atrophy were associated with better FrSBe scores.

An increased apathy score was associated ($p_{\text{uncorrected}} < 0.001$) with reduced gray matter density in a distributed network of brain areas, located in the dorsolateral prefrontal cortex (DLPFC) bilaterally, right lateral orbitofrontal cortex (OFC), right temporoparietal junction, anterior cingulate cortex (ACC), and right putamen (table 2, figure 1, and figure e-2). Of those, the right DLPFC also survived the whole-brain threshold of $p_{\text{FWE-corrected}} < 0.05$. From the stepwise multiple regression analysis, a significant model emerged explaining 32.7% of the variance of the FrSBe Apathy subscale ($F_{(3,58)} = 10.858$, $p < 0.0005$, adjusted $R^2 = 0.327$). The gray matter den-

Figure 1 Neural correlates of apathy

Regions of reduced gray matter density associated with apathy in frontotemporal dementia patients. Right dorsolateral prefrontal cortex, anterior cingulate, and putamen are visualized ($p < 0.001$, uncorrected; minimum cluster size 30 voxels). Coordinates are in Talairach space.

Figure 2 Neural correlates of disinhibition

Regions of reduced gray matter density associated with disinhibition in frontotemporal dementia patients. Hippocampus, amygdala, and ventral striatum (nucleus accumbens) are visualized ($p < 0.001$, uncorrected; minimum cluster size 30 voxels). Coordinates are in Talairach space.

sity peak values in the right DLPFC ($\beta = -0.41$, $p < 0.001$), left DLPFC ($\beta = -0.24$, $p < 0.05$), and Mattis-DRS scores ($\beta = -0.24$, $p < 0.05$) were predictor variables in this model.

An increased disinhibition score was associated ($p_{\text{uncorrected}} < 0.001$) with gray matter loss in an extended portion of the right medial temporal lobe, including amygdala and hippocampus (also surviving the whole-brain $p_{\text{FWE-corrected}} < 0.05$), in the right nucleus accumbens (ventral striatum), and in the right superior temporal sulcus (table 2, figure 2, and figure e-2). From the stepwise multiple regression analysis, a significant model emerged that explained 32.1% of the variance of the Disinhibition score ($F_{(2,59)} = 15.437$, $p < 0.0005$, adjusted $R^2 = 0.321$). The gray matter density peak values in the amygdala ($\beta = -0.43$, $p < 0.0005$) and in the accumbens ($\beta = -0.30$, $p < 0.01$) were significant predictor variables of the Disinhibition score in this model.

When the correlational analyses were limited to the regions resulting from the comparison with the controls (FWE corrected), the same regions were involved (table e-2).

DISCUSSION Our findings demonstrated that prefrontal cortex, medial temporal structures, and basal ganglia are differentially involved in determining the apathetic and disinhibited profiles of FTD.

In a previous study, a VBM correlation analysis was performed in patients with different diagnoses of dementia to correlate subscores of the NPI with atrophy.¹⁹ The NPI subscore for apathy correlated with volume loss in the medial superior frontal gyrus, and the NPI subscore of disinhibition correlated with atrophy in the subgenual cingulate cortex. Our study differs from that study in patient population, because we focused on a homogeneous group that included only FTD patients. In addition, the FrSBe Apathy and Disinhibition subscales are better suited to identify the neural correlates of complex behavioral profiles based on the co-occurrence of several specific

behaviors, whereas in the NPI, the same terms refer to sub-items measuring single specific behaviors. Therefore, although the NPI might have provided more specificity in characterizing distinct behaviors, the FrSBe better suited the purpose of the present study, which was to identify the neural correlates of complex behavioral profiles based on the aggregation of a set of behaviors. An exploratory principal factor analysis of the FrSBe²³ confirmed that the 46 items describing different behaviors consistently loaded together on each of the three subscales that were proposed on the basis of the anatomofunctional interpretation of prefrontal-subcortical circuits.^{5,6} Therefore, the FrSBe is more descriptive of disinhibited and apathetic *types*, whereas the NPI more precisely refers to apathy and disinhibition as specific behaviors. This difference may have contributed to the dissimilarities of our results with previous findings.

Consistent with previous studies on FTD and brain-injured patients,^{26,27} our results demonstrated a predominant involvement of the right hemisphere in both behavioral abnormalities, supporting the notion that the right hemisphere has a critical role in complex social behaviors.

The severity of the score measuring apathy was associated with atrophy in different prefrontal regions—including DLPFC, OFC, and ACC—and in the putamen. The DLPFC has a role in executive functions such as planning, rule finding, and problem solving.^{28,29} The impairment of those functions results from difficulty in elaborating and executing goal-directed behaviors, a deficit that may also be reflected in a type of apathy that has been described as “cognitive inertia.”³⁰ Interestingly, the FrSBe Apathy subscale score was significantly predicted by a model that included not only peak values of gray matter density in the DLPFC bilaterally, but also a measure of dementia severity (Mattis-DRS). According to the anatomic organization of frontal-subcortical circuits,^{6,31} the DLPFC projects to the putamen that

was similarly associated with apathy in our study. In addition, our results showed the involvement of the ACC, which is part of a circuit important in the integration of emotional information with motivation³² and has been repeatedly associated with apathy and disorders characterized by decreased spontaneous goal directed behavior, including akinetic mutism.³³

The severity of the score measuring disinhibition was associated with gray matter loss in right medio-temporal structures (amygdala and hippocampus) and right nucleus accumbens (ventral striatum). The multiple regression confirmed that peak values of atrophy in these regions significantly predict the variance of the FrSBe Disinhibition subscale. Those structures are densely interconnected and are part of the mesolimbic dopaminergic system, which plays a key role in motivated and emotional behavior.³⁴ The amygdala has a demonstrated role in fear conditioning and, more generally, in the detection of environmental cues such as threat and danger.³⁵ The accumbens (ventral striatum) plays a key role in the dopaminergic system responsible for reinforcement and reward, as well as for goal-directed behaviors such as compulsive drug seeking in addicts.³⁴ In addition, functional neuroimaging studies have demonstrated its role in the expectation of the rewarding value of complex socially meaningful stimuli, such as commercial products.³⁶

The association of mainly temporal structures with the FrSBe Disinhibition subscale seems consistent with the behavioral deficits shown by patients with focal temporal lesions or with temporal lobe epilepsy, in which an extensive range of behavioral symptoms, including mania, euphoria, and aggressive behaviors, have been described.³⁷ These deficits are often interpreted as reflecting the connections of the temporal lobe with orbitofrontal regions and not as a consequence of the loss of specific functions represented in the temporal lobes.³⁷ According to one functional interpretation of frontal-subcortical circuits,³¹ temporolimbic structures and nucleus accumbens are part of the orbitofrontal circuit, whose dysfunction is characterized by disinhibition syndromes including irritability, impulsivity, and undue familiarity. This has been interpreted as the consequence of loss of inhibition by the frontal monitoring system on the limbic system that is responsible for instinctual behaviors. But in our study, there were no frontal areas in which gray matter loss was specifically associated with the severity of disinhibition when controlling for apathy, dementia severity, and other demographic variables. Therefore, our results suggest an alternative interpretation: that disinhibited behaviors may result from impaired risk perception and reward/punishment attribution mechanisms and may occur independently from prefrontal dysfunction. This supports the view

that the role of prefrontal structures important in executive functions and motivation and the role of temporolimbic structures involved in reward and emotional processing need to be integrated³⁸ to properly perform complex social behaviors.

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