Evidence of White Matter Changes on Diffusion Tensor Imaging in Frontotemporal Dementia

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Background: Two major clinical variants of frontotemporal dementia (FTD) have been described: frontal variant (fvFTD) and temporal variant (tvFTD).

Objective: To analyze white matter (WM) and gray matter (GM) tissue organization in patients with fvFTD and tvFTD by means of diffusion tensor imaging and voxel-based morphometry, and the correlations with neuropsychological and behavioral variables.

Design and Setting: Frontotemporal dementia clinic–based cohort and structural magnetic resonance imaging acquisition for voxel-based morphometry and diffusion tensor imaging measurements. Abnormalities were detected by a comparison with healthy control subjects. These variables were also correlated with clinical scores.

Patients: Thirty-six patients (28 with fvFTD and 8 with tvFTD) in early disease stage and 23 healthy controls who underwent standardized clinical and neuropsychological evaluation and magnetic resonance imaging.

Interventions: Diffusion tensor imaging and voxel-based morphometry.

Main Outcome Measures: Neuroimaging analyses resulted in localized GM atrophy and reductions of white matter densities; the latter correlated with behavioral scores.

Results: Voxel-based morphometry analysis showed separate patterns of GM atrophy in the 2 groups. Diffusion tensor imaging showed different WM reduction patterns in patients with fvFTD and tvFTD. The fvFTD group showed a selective WM reduction in the superior longitudinal fasciculus, interconnecting the frontal and occipital and the temporal and parietal regions. Conversely, patients with tvFTD were characterized by WM reductions in the inferior longitudinal fasciculus, which affected the connections between anterior temporal and frontal regions. The WM reductions in fvFTD paralleled both behavioral disturbances measured by Frontal Behavioral Inventory and neuropsychological deficits affecting frontal functions.

Conclusions: The fvFTD and tvFTD variants are associated not only with selective local GM reductions but also with significant WM damage in early disease phase. The different WM patterns contribute to the different clinical syndromes in FTD and could be responsible for the further progression of atrophy in the later disease stages.

Arch Neurol. 2007;64:246-251

FRONTOTEMPORAL DEMENTIA (FTD) is a neurodegenerative disorder localized primarily in the frontal lobes and in the anterior portions of the temporal lobes.[1] Although often considered a unitary syndrome, numerous studies have characterized 2 major presentations of FTD, which reflect the predominant sites of abnormality. Progressive change in personality and behavior coupled with executive dysfunction has been associated with the frontal variant of FTD (fvFTD), whereas patients with the temporal lobe variant (tvFTD) often demonstrate a progressive fluent aphasia or breakdown in semantic knowledge.[2]

Recently, a few studies have proposed voxel-based morphometry (VBM) as a highly useful method for describing brain changes in FTD and among FTD subtypes.[3] Mainly because of the low correlation between white matter (WM) T1 signal intensities and integrity, VBM has proved to be inefficient in detecting WM.[4]

In contrast to this approach based on T1-weighted imaging, diffusion tensor imaging (DTI) provides more subtle information about WM tissue composition,[5] allowing identification of fiber tracts in vivo.[6] While DTI has been successfully performed in neurodegenerative diseases,[7] this technique has been applied in only 1 single-case postmortem study on FTD, to our knowledge.[8]

Therefore, the aim of the present study was to use DTI to analyze the WM characteristics in fvFTD and tvFTD. We also computed the correlations between WM changes and neuropsychological and behavioral performance.

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METHODS

SUBJECTS

All recruited patients fulfilled international consensus criteria for FTD, with a subsequent subdivision into 2 major clinical subtypes: frontal variant FTD (fvFTD) and temporal variant FTD (tvFTD).[2,9] All subjects underwent clinical evaluation, routine laboratory examination, and brain perfusion study with technetium Tc 99m bicisate single-photon emission computed tomography.

The diagnostic assessment involved a review of full medical history, a semistructured neurologic examination including motor impairment assessment by the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS–III), and a neuropsychological evaluation. Two independent and experienced reviewers (B.B. and A.P.) made the diagnosis, and only patients who were diagnosed as fulfilling FTD criteria by both reviewers were enrolled.

We examined the different cognitive domains by using a standardized neuropsychological assessment other than the screening test for dementia (Mini-Mental State Examination [MMSE]), such as tests of nonverbal reasoning (Raven Colored Progressive Matrices), verbal fluency with phonemic and semantic cues, constructional abilities and visual spatial recall (Rey-Osterrieth Complex Figure Test and Trail-Making Test A), long-term memory for prose (Short Story), verbal short-term memory (Digit Span), executive functions (Trail-Making Test B), auditory language comprehension (Token Test), and imitation (De Renzi Imitation Test).[10] Instrumental activities of daily living and basic activities of daily living were assessed as well. Behavioral and psychiatric disturbances were evaluated by the Neuropsychiatric Inventory and Frontal Behavioral Inventory (FBI).[11]

A group of 23 healthy subjects (9 men and 14 women; mean±SD age, 65.8±6.6 years) were recruited among patients' spouses or relatives, studied with magnetic resonance (MR) imaging, and included in the VBM and DTI analyses as normal control subjects. They were interviewed and assessed for neurologic or cognitive dysfunction (MMSE score, >27; Clinical Dementia Rating Scale score, 0) and were subject to the same exclusion criteria as the patient groups.

The work was conducted in accordance with local clinical research regulations and conformed to the Helsinki Declaration. A signed informed consent was obtained from all subjects.

EXCLUSION AND INCLUSION CRITERIA

Stringent exclusion criteria were applied as follows: (1) cerebrovascular disorders, hydrocephalus, and intracranial mass, documented by MR imaging; (2) a history of traumatic brain injury or another neurologic disease; (3) significant medical problems such as poorly controlled diabetes mellitus or hypertension or cancer within the past 5 years; and (4) major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, or mental retardation according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.[12]

Inclusion criteria were the following: (1) mild cognitive decline (MMSE score, ≥17) and (2) follow-up for at least 1 year after enrollment and diagnosis confirmed. All included subjects were right-handed.

MR IMAGING DATA ACQUISITION

The MR imaging was performed on a 1.5-T imager (Symphony; Siemens, Erlangen, Germany).

For VBM analysis, 3-dimensional magnetization–prepared rapid gradient echo T1-weighted images were acquired by means of the following settings: echo time, 3.93 milliseconds; repetition time, 2010 milliseconds; flip angle, 15°, and field of view, 250 mm. This yielded 176 contiguous 1-mm-thick sections.

Diffusion tensor imaging was performed by means of echo-planar imaging at 1.5 T with standard head coil for signal reception. The DTI axial sections were obtained with the following settings: matrix, 128×128; echo time, 122 milliseconds; repetition time, 6600 milliseconds; flip angle, 15°; field of view, 220 mm; no gap (5-mm thickness); and voxel size, 1.7×1.7×5 mm. Three acquisitions were averaged. Diffusion weighting was performed along 6 independent directions with a b value of 1000 seconds/mm^2. A T2-weighted image with no diffusion weighting was also obtained (b=0).

IMAGE ANALYSIS

Both preprocessing and statistical analyses were implemented in the SPM2 software package (Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 6.5.1 (MathWorks, Natick, Mass).[13] Optimized VBM analysis was performed according to Good and colleagues,[14] as previously published.[7]

For DTI, the fractional anisotropy (FA) (an index of the directional selectivity of water diffusion) was determined for each voxel by means of BrainVisa 1.6 software.[15] The FA is a quantitative measure of diffusion anisotropy, intrinsic to the tissue under examination and independent of the orientation of the subject in the magnet.

A customized template was obtained by taking the average of all participants' T2 (b=0) images, previously normalized to the echo-planar imaging template within MNI (Montreal Neurological Institute) standard stereotactic space.

We calculated the normalization variables that best fit each T2 image with a customized echo-planar imaging template, which were then applied to FA maps and to T2 images.

The T2 normalized images were then segmented into gray matter (GM), WM, and cerebrospinal fluid. A WM binary mask was created from the WM segments obtained in the previous step and applied to each subject's normalized FA map to include only the voxels belonging to the WM regions in the statistical analysis. The masked normalized FA maps were smoothed with a 10-mm full-width half-maximum kernel. The smoothed WM segments were then statistically tested by means of a general linear model based on gaussian field theory.

The FA differences between groups were assessed by a 2-sample *t* test statistical design. We accepted a statistical threshold of $P<.05$ (familywise error [FWE]).

CORRELATION ANALYSIS OF FA AND NEUROPSYCHOLOGICAL AND BEHAVIORAL ASSESSMENT

The relationship between FA and neuropsychological and behavioral assessment scores was further investigated. We used regions of interest positioned on the FA map, which included the superior longitudinal fasciculus as shown in the comparison between the fvFTD and control groups.

The FA data were correlated with all demographic variables and with the neuropsychological and behavioral tests included in the standardized assessment by using the Spearman rank correlation analysis and subsequent multiple regression analysis to further analyze the relationship between FA and the different predictors (SPSS 11.5; SPSS Inc, Chicago, Ill).

Table 1. Demographic Characteristics in Control Subjects and Patients With FTD

Variable	Controls	fvFTD	tvFTD	*P* Value
N	23	28	8	NA
Age, mean ± SD, y	65.8 ± 6.6	66.4 ± 7.0	67.5 ± 8.2	.72*
Sex, No. F/M	14/9	15/13	8/0	.001†
Education, mean ± SD, y	8.0 ± 3.2	7.7 ± 3.2	8.5 ± 3.6	.58*
Age at onset, y	NA	63.5 ± 7.9	64.4 ± 8.8	.81‡

Abbreviations: FTD, frontotemporal dementia; fvFTD, frontal variant of FTD; NA, not applicable; tvFTD, temporal variant of FTD.
*One-way analysis of variance.
†χ^2 Test among control, fvFTD, and tvFTD groups.
‡Paired *t* test between fvFTD and tvFTD groups.

Table 2. Clinical and Neuropsychological Characteristics in Patients With FTD

Variable	Normative Cutoff Score*	Score, Mean ± SD		*P* Value†
		fvFTD	tvFTD	
MMSE	>24	23.0 ± 3.9	22.3 ± 3.7	.21
UPDRS-III	0.0	8.6 ± 8.0	3.5 ± 3.7	.09
IADL (lost)	0.0	1.4 ± 2.1	2.6 ± 2.6	.21
BADL (lost)	0.0	0.4 ± 1.0	0.3 ± 0.7	.62
FBI A	0.0	10.6 ± 7.2	12.1 ± 6.5	.59
FBI B	0.0	7.1 ± 6.5	4.4 ± 3.4	.27
FBI AB	0.0	17.6 ± 12.4	16.5 ± 8.4	.81
NPI, total	0.0	17.4 ± 14.0	12.6 ± 7.1	.36
De Renzi Imitation Test	>53.0	67.8 ± 6.7	67.9 ± 3.9	.78
Short Story	>7.50	8.6 ± 5.1	4.5 ± 1.7	.05
Raven Colored Progressive Matrices	>18.85	22.4 ± 5.4	25.9 ± 4.1	.66
Rey-Osterrieth Complex Figure Test, copy	>32.0	25.1 ± 9.8	27.4 ± 11.6	.62
Rey-Osterrieth Complex Figure Test, recall	>10.30	12.1 ± 7.2	13.4 ± 4.2	.73
Fluency, phonemic	>17.35	23.6 ± 12.0	18.2 ± 9.6	.19
Fluency, semantic	>7.50	9.1 ± 3.9	6.2 ± 2.3	.05
Digit Span	>3.75	5.5 ± 1.7	5.0 ± 2.3	.54
Token Test	>26.50	28.8 ± 5.9	25.7 ± 2.7	.31
Trail-Making Test A, s	<94.0	90.9 ± 45.6	94.2 ± 52.0	.56
Trail-Making Test B, s	<283.0	298.0 ± 152.4	160.4 ± 83.5	.09

Abbreviations: BADL, basic activities of daily living; FBI, Frontal Behavioral Inventory; FTD, frontotemporal dementia; fvFTD, frontal variant of FTD; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; tvFTD, temporal variant of FTD; UPDRS, Unified Parkinson's Disease Rating Scale.
*Cutoff scores according to Italian normative data.
†Mann-Whitney test.

RESULTS

SUBJECTS

Thirty-six patients with FTD (28 with fvFTD and 8 with tvFTD) entered the study. Demographic and clinical characteristics of the fvFTD and tvFTD subgroups and age-matched controls are reported in **Table 1**. The fvFTD and tvFTD groups did not differ in terms of age, age at onset, or education, but they differed in sex.

Global cognitive decline (MMSE) and functional impairment (instrumental activities of daily living and basic activities of daily living) were compared in the 2 subgroups (**Table 2**). Table 2 also reports neuropsychological and behavioral assessment scores in patients with fvFTD and tvFTD. Those with fvFTD mainly showed behavioral disturbances and pathological scores in the Trail-Making Test B, which taps executive functions. The patients with tvFTD showed pathological performances in Category Fluency, Token Test, and Short Story, underlying language deficits; behavioral disturbances were also evident, but the pattern did not differ from that of the fvFTD group.

VBM ANALYSIS

Patients with fvFTD compared with controls showed significant GM atrophy in the dorsolateral frontal cortex, anterior cingulate cortex, insula, superior temporal gyrus, and thalamus bilaterally ($P<.05$, FWE corrected). In patients with tvFTD, there was a prevalent GM reduction in the left hemisphere involving the middle and inferior temporal gyrus and the superior frontal and orbitofrontal gyrus; GM was also reduced in the temporal pole and superior temporal gyrus bilaterally ($P<.05$, FWE corrected).

The VBM analysis did not show any significant WM difference between patients with fvFTD and controls. The

Table 3. Location of Peaks of Regional Reduction of Fractional Anisotropy in Patients With fvFTD and tvFTD Compared With Control Subjects*

White Matter Fiber Track	Peak MNI Coordinates, mm x	y	z	T Score	*z* Score
		Controls vs fvFTD†			
Right superior longitudinal fasciculus	22	–40	38	5.91	5.08
	28	–28	42	5.81	5.02
	28	–54	28	5.33	4.69
	44	–22	20	5.64	4.90
	44	–8	14	5.55	4.84
	30	10	22	5.53	4.83
	26	16	36	5.33	4.69
		Controls vs tvFTD†			
Right inferior longitudinal fasciculus	30	4	–34	7.49	5.50
Left inferior longitudinal fasciculus	–38	–4	–26	8.59	5.96
	–42	–24	–14	8.49	5.93
	–36	–54	2	6.82	5.19
Right inferior fronto-occipital fasciculus	26	26	16	6.73	5.15
Left inferior fronto-occipital fasciculus	–28	32	14	8.15	5.79
	–30	14	28	7.40	5.46
	–26	32	–8	6.42	4.99
Left superior longitudinal fasciculus	–42	–32	22	5.97	4.76
Left callosal radiations	–18	–48	38	6.83	5.20
	–18	–54	30	6.77	5.17
	–40	–50	24	5.99	4.77

Abbreviations: fvFTD, frontal variant of frontotemporal dementia; MNI, Montreal Neurological Institute; tvFTD, temporal variant of frontotemporal dementia.
*$P<.05$, familywise error corrected. The x, y, and z values localize the areas of fractional anisotropy reduction according to the MNI stereotactic coordinates.
†Only peaks with the highest significance are reported.

WM comparison did, however, show a significant difference in the left inferior longitudinal fasciculus in patients with tvFTD ($P<.05$, FWE corrected).

No regions of WM or GM reductions were observed in controls compared with patients with fvFTD or tvFTD at the preestablished threshold ($P<.05$, FWE corrected).

DTI ANALYSIS

The DTI analysis showed significant and extensive FA changes in the right superior longitudinal fasciculus in patients with fvFTD compared with controls ($P<.05$, FWE) (**Table 3** and **Figure 1**A). At a lower statistical threshold ($P<.001$, uncorrected) the involvement was bilateral.

Patients with tvFTD showed FA reduction in the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus bilaterally, and in the left callosal radiations and the left superior longitudinal fasciculus ($P<.05$, FWE) (Table 3 and Figure 1B).[16]

To rule out WM differences that could be ascribed to sex, we reran the analysis including sex as a nuisance variable in the design matrix. The results did not change, even at a lower threshold ($P<.001$, uncorrected).

CORRELATION ANALYSIS OF FA AND NEUROPSYCHOLOGICAL AND BEHAVIORAL ASSESSMENT

No significant correlation between FA and demographic characteristics was found.

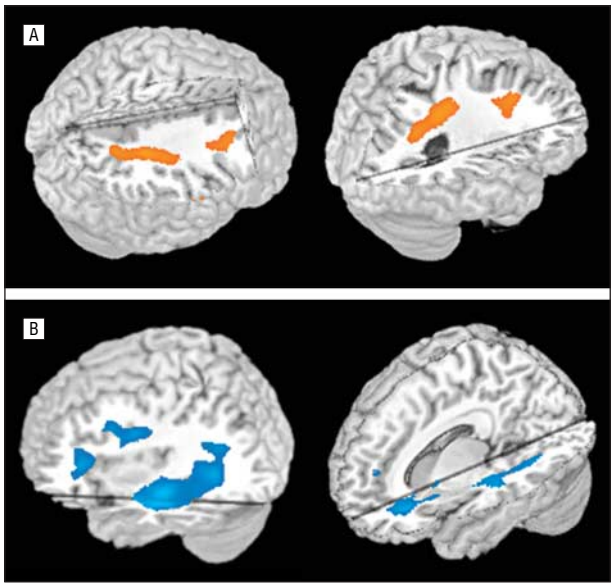

Figure 1. Reduction in fractional anisotropy in patients with frontal variant (A) and temporal variant (B) of frontotemporal dementia compared with controls, superimposed on 3-dimensional brain templates. A, Right superior longitudinal fasciculus. B, Left inferior longitudinal fasciculus, left superior longitudinal fasciculus, and callosal radiations. The threshold was set at $P<.05$, familywise error. See Table 3 for coordinates.

In the fvFTD subgroup, an inverse correlation was found between FA in the superior longitudinal fasciculus (mean ± SD, 0.93 ± 0.07) and FBI A ($r=-0.49$, $P=.01$), FBI B ($r=-0.48$, $P=.01$), and FBI AB ($r=-0.50$, $P=.009$). The analysis of FBI subitems showed that inflexibility

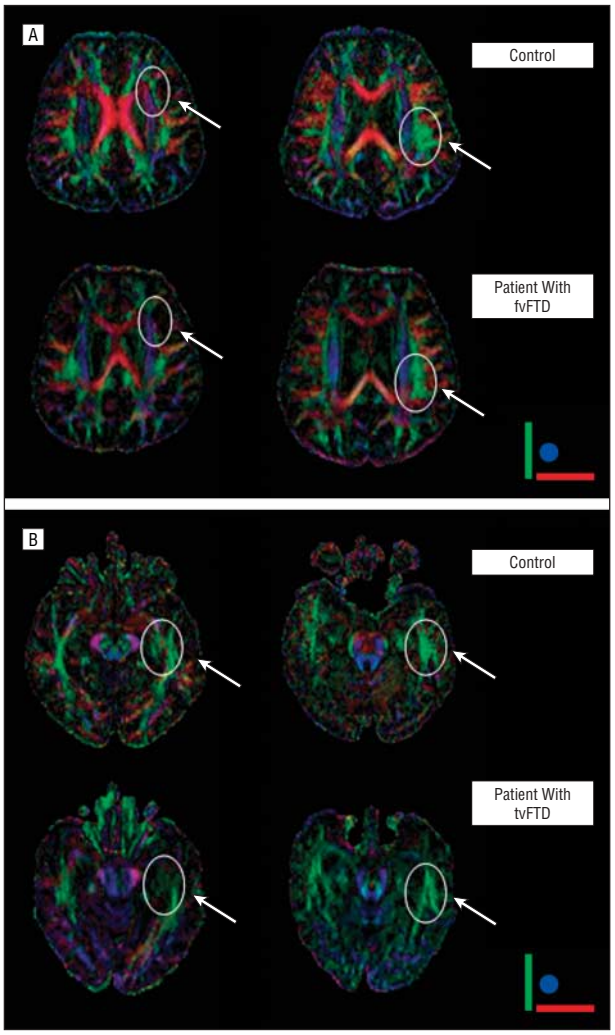

Figure 2. Diffusion tensor imaging red-green-blue maps in a representative control subject and patients with frontal variant and temporal variant of frontotemporal dementia (fvFTD and tvFTD, respectively), illustrating the selective fiber tract changes. A, Red-green-blue maps in a representative control subject (first row) and a patient with fvFTD (second row), highlighting the reduction in the superior longitudinal fasciculus in the latter (arrows). B, Red-green-blue maps in a representative control subject (first row) and a patient with tvFTD (second row), highlighting the reduction in the inferior longitudinal fasciculus in the latter (arrows). Green was assigned to anterior-posterior, red to left-right, and blue to craniocaudal connection.[16]

($r=-0.50$, $P=.009$), personal neglect such as lack of personal hygiene ($r=-0.56$, $P=.003$), disorganization in planning and organizing complex activity ($r=-0.46$, $P=.02$), impulsivity or poor judgment ($r=-0.45$, $P=.02$), and utilization behavior ($r=-0.49$, $P=.01$) were significantly related to FA reduction; the worse the scores in behavioral disturbances, the lower the FA in the superior longitudinal fasciculus. On the other hand, the other FBI subitems, such as those related to language disturbances, behavioral disturbances, hoarding, or perseverations, were not significantly correlated with FA reduction. Alien hand, roaming, incontinence, and hyperorality were not considered because they were rare in our sample.

A multiple regression analysis of significantly associated FBI subitems demonstrated that all of them were independently related to FA reduction.

The same analysis was made by considering all the neuropsychological tests (see those listed in Table 2). Only the Trail-Making Test B scoring was inversely correlated with FA in the superior longitudinal fasciculus (Spearman rank correlation analysis, $r=-0.41$, $P=.04$).

In patients with tvFTD, the correlations between FA in the inferior longitudinal fasciculus and neuropsychological and behavioral variables were not investigated because of the small sample size.

DTI IN SINGLE SUBJECTS

Selective reduction of WM bundles, ie, superior longitudinal fasciculus and inferior longitudinal fasciculus, was illustrated in 2 individual representative patients with fvFTD and tvFTD.

A healthy control subject (60 years old; MMSE score, 30/30; UPDRS-III score, 0), a patient with fvFTD (59 years old; MMSE score, 26/30; UPDRS-III score, 9), and a patient with tvFTD (58 years old; MMSE score, 27/30; UPDRS-III score, 0) were chosen.

Fiber tracking was obtained with the FACT (fiber assignment by continuous tracking) algorithm implemented in BrainVisa software, and red-green-blue maps were reconstructed. According to previously published data,[17] green was assigned to anteroposterior, red to left-right, and blue to craniocaudal connection (**Figure 2**).

COMMENT

The rapid development of MR imaging techniques, in particular DTI, has renewed interest and opened new avenues for analyzing WM in the living human brain.[18] Diffusion tensor imaging detects microstructural alterations in WM by measuring the directionality of molecular diffusion and allows the exploration of the entire brain. Well-organized WM tracts have high FA because diffusion is deeply constrained by the tract's cellular organization. As WM is damaged, FA decreases because of decreased anisotropic diffusion.

In this study, the combination of DTI with FA and statistical parametric mapping allowed us to gain further insight into the organization of microstructural integrity of WM tracts, and into the directionality of molecular diffusion in patients with well-defined FTD at the early disease stage. Moreover, VBM data were broadly consistent with those described in previous literature findings.[3]

We found a significant and extensive WM reduction in the superior longitudinal fasciculus, which interconnects dorsolateral frontal lobe and posterior associative areas (occipital, parietal, and temporal) in patients with fvFTD. On the other hand, patients with tvFTD showed different WM reductions that were located bilaterally in the inferior longitudinal fasciculus, interconnecting the anterior temporal lobe and posterior occipital pole in extrastriatal cortical regions, and in the inferior fronto-occipital fasciculus, interconnecting the inferolateral and dorsolateral frontal cortices and both the temporal and occipital cortices. In addition, in patients with tvFTD the callosal radiations and the left superior longitudinal fasciculus were reduced (see Figure 1). The involvement

of WM bundles is consistent with GM atrophy measured with VBM, affecting mainly the frontal regions in fvFTD and the temporal regions in tvFTD.

These findings support the theory that WM changes are a crucial hallmark in the pathological characteristics of FTD and parallel recent autopsy evidence of tau deposition in tauopathies, not only in GM but in WM as well.[19]

The DTI measures were also very precise in providing a clear-cut description of WM abnormalities and in differentiating patients with fvFTD and tvFTD.

Our results also suggest that WM networks, along with GM involvement, are likely related to the different clinical symptoms associated with fvFTD and tvFTD. In fact, the amount of WM reduction in superior longitudinal fasciculus correlated with the behavioral deficits, as measured by the FBI, characteristic of these patients. A significant relationship between FA decrease and a test assessing executive functions, such as Trail-Making Test B, was also demonstrated.

Most studies have focused on frontotemporal lobe abnormalities for differentiating fvFTD and tvFTD, although the possible involvement of more posterior connections has yet to be investigated. The present data indicate an overall impairment of fiber bundles connecting the frontotemporal to occipital lobes, thus signaling a wider WM involvement compared with the more focal frontotemporal GM atrophy. Further studies are needed to support our results in larger samples, in neuropathologically confirmed series, and in different disease stages.

Accepted for Publication: June 28, 2006.
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Financial Disclosure: None reported.
Acknowledgment: We thank patients and their families for the time and effort they have dedicated to our research. We also thank Rafael Alonso, PhD, for his helpful comments.

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