White Matter Damage in Frontotemporal Lobar Degeneration Spectrum

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White matter (WM) tract damage was assessed in patients with the behavioral variant frontotemporal dementia (bvFTD) and the 3 primary progressive aphasia (PPA) variants and compared with the corresponding brain atrophy patterns. Thirteen bvFTD and 20 PPA patients were studied. Tract-based spatial statistics and voxel-based morphometry were used. Patients with bvFTD showed widespread diffusion tensor magnetic resonance imaging (DT MRI) abnormalities affecting most of the WM bilaterally. In PPA patients, WM damage was more focal and varied across the 3 syndromes: left frontotemporoparietal in nonfluent, left frontotemporal in semantic, and left frontoparietal in logopenic patients. In each syndrome, DT MRI changes extended beyond the topography of gray matter loss. Left uncinate damage was the best predictor of frontotemporal lobar degeneration diagnosis versus controls. DT MRI measures of the anterior corpus callosum and left superior longitudinal fasciculus differentiated bvFTD from nonfluent cases. The best predictors of semantic PPA compared with both bvFTD and nonfluent cases were diffusivity abnormalities of the left uncinate and inferior longitudinal fasciculus. This study provides insights into the similarities and differences of WM damage in bvFTD and PPA variants. DT MRI metrics hold promise to serve as early markers of WM integrity loss that only at a later stage may be detectable by volumetric measures.

Keywords: diffusion tensor MRI, frontotemporal dementia, frontotemporal lobar degeneration, primary progressive aphasia, white matter

Introduction

Frontotemporal lobar degeneration (FTLD) spectrum of disorders includes 2 major clinical presentations: a behavioral variant frontotemporal dementia (bvFTD) and a language variant (Neary et al. 1998). bvFTD presents with marked changes in personality and behavior (Neary et al. 1998) and, pathologically, is associated with either tau- or TAR DNA-binding protein 43 (TDP-43)-positive inclusions (Mackenzie et al. 2010). In the language variant, known as primary progressive aphasia (PPA), a prominent isolated language deficit is the dominant feature during the initial phase of the disease (Mesulam 2001). Distinct profiles of language impairment define the 3 PPA variants (Gorno-Tempini et al. 2011): nonfluent/agrammatic, semantic, and logopenic. The nonfluent variant is most commonly associated with tau pathology, while the semantic one is usually a TDP-43 proteinopathy (Mesulam et al. 2008). Alzheimer’s disease (AD) is the most likely underlying pathology in the more controversial logopenic variant, although FTLD-TDP changes can also be found (Mesulam et al. 2008).

The clinical and the pathological heterogeneity of FTLD poses a significant diagnostic challenge, and the in vivo phenotypic characterization of these patients can be improved by supplementing the clinical evaluation with imaging biomarkers. Structural magnetic resonance imaging (MRI) showed that each syndrome is associated with a specific pattern of atrophy (Mummery et al. 2000; Gorno-Tempini et al. 2008; Rohrer et al. 2009). White matter (WM) alterations are also a major pathological characteristic in FTLD (Schofield et al. 2003; Neumann et al. 2007). By measuring directional changes in water diffusivity, diffusion tensor (DT) MRI allows to investigate brain WM microstructure (Basser et al. 1994). bvFTD patients showed DT MRI changes in the frontal and temporal WM (Borroni et al. 2007; Matsuo et al. 2008; Zhang et al. 2009; Whitwell et al. 2011). However, only limited evidence is available regarding WM damage in PPA. A few studies showed that the semantic variant is associated with severe damage to temporal lobe tracts (Borroni et al. 2007; Matsuo et al. 2008; Agosta et al. 2010; Whitwell et al. 2011). To our knowledge, only a few DT MRI studies investigated WM damage in the nonfluent (Galantucci et al. 2011; Whitwell et al. 2011) and logopenic (Galantucci et al. 2011) variants, but since a region of interest (ROI)- or tractography-based approach was used, the overall pattern of WM damage was not defined.

In this study, we employed tract-based spatial statistics (TBSS): 1) to investigate WM tract integrity in patients with a clinical diagnosis of bvFTD and the 3 PPA variants and 2) to compare these results with the corresponding patterns of brain atrophy. We hypothesized that each syndrome would be associated with a distinct pattern of damage, involving specific networks that are critical to behavior and language processing, which are impaired in these patients. We also predicted that each syndrome would have the most severe WM damage to those tracts connecting atrophied gray matter (GM) regions. Finally, we wished to quantify the predictive ability of DT MRI variables in distinguishing each FTLD-related syndrome from healthy individuals and each other.

Materials and Methods

Subjects

Right-handers (Oldfield 1971) native Italian-speaking patients with bvFTD (Neary et al. 1998) and patients with PPA (Gorno-Tempini et al. 2011) were recruited at the Department of Neurology, Scientific...
Institute and Hospital San Raffaele, Milan. Patients received a comprehensive evaluation including neurological history and examination, neuropsychological testing, genetic analysis, and neuroimaging. Clinical assessments were performed by experienced neurologists blinded to MRI results. History was taken with a structured interview from patients’ relatives. Patients were diagnosed with bvFTD according to established criteria (Neary et al. 1998). A diagnosis of PPA required progressive deterioration of speech and/or language functions and that deficits be largely restricted to speech and/or language for at least 2 years (Mesulam 2001). Patients were then diagnosed with a particular PPA variant (i.e., nonfluent, semantic, and logopenic) based on diagnostic guidelines recently developed by an international group of PPA investigators (Gorno-Tempini et al. 2011). Right-handers (Oldfield 1971), native Italian-speaking healthy controls were recruited among spouses of patients and by word of mouth. Healthy controls underwent a multidimensional assessment, including neurological and neuropsychological evaluation, and were included in the study only when all of them were normal. Subjects were excluded if they had: 1) a family history of dementia or FTLD-related disorders; 2) significant medical illnesses or substance abuse that could interfere with cognitive functioning; 3) any other major systemic, psychiatric, or neurological illnesses; and 4) other causes of focal or diffuse brain damage, including lacunae, and extensive cerebrovascular disorders at routine MRI.

We studied 33 patients: 13 bvFTD, 9 nonfluent, 7 semantic, and 4 logopenic (Table 1). Twenty-five healthy ages were matched with the bvFTD group (HCbvFTD) and 27 healthy controls were age and sex matched with the PPA group (HCPPA). Because clinical syrdomic diagnoses can sometimes be erroneous, we also collected in some patients additional data, which were not used for subject selection. One patient with the nonfluent variant had comorbid motor neuron disease, which strongly supports an underlying diagnosis of FTLD with TDP-43 inclusions (Hodges et al. 2004). Nine bvFTD and 17 PPA patients were screened for progranulin mutations. One patient with bvFTD and 3 patients with the nonfluent variant were found to harbor a mutation in the progranulin gene. No mutations were identified among the 3 patients tested for microtubule-associated protein tau mutations. Approval was received from the local ethical standards committee on human experimentation and written informed consent was obtained from all subjects participating in the study.

**Cognitive Assessment**

Neuropsychological assessment was performed by an experienced neuropsychologist blinded to the MRI results and evaluated: 1) global cognitive functioning with the Mini-Mental State Examination (Folstein et al. 1975); 2) memory function with verbal and spatial span (Orsini et al. 1987) and Rey’s figure delayed recall test (Caffarra et al. 2002); 3) frontal-executive functions with the Raven’s colored progressive matrices (Basso et al. 1987) and the digit span backward (Wechsler 1981); 4) language functions with the phonemic and semantic fluency (Novelli et al. 1986) and token tests (De Renzi and Vignolo 1962; Spinler and Tognoni 1987); 5) visuospatial abilities with the Rey’s Figure Copy Test (Caffarra et al. 2002); and 6) attention with attentive matrices (Spinler and Tognoni 1987). Patients meeting PPA criteria also underwent a comprehensive language and speech evaluation using the Battery for Analysis of Aphasias (Miceli et al. 1994). Scores on neuropsychological tests were age, sex, and education corrected by using related normative values whenever available. The neuropsychological profiles of bvFTD and PPA patients are shown in Supplementary Table 1.

**MRI Acquisition**

Brain MRI scans were obtained using a 3.0-T scanner (Intera, Philips Medical Systems, Best, the Netherlands). The following sequences were obtained from all subjects: 1) $T_2$-weighted spin echo (SE) (repetition time [TR] = 3500 ms, echo time [TE] = 85 ms, echo train length = 15, flip angle = $90^\circ$), 22 contiguous 5-mm-thick axial slices with a matrix size $= 512 \times 512$, field of view [FOV] = 230 $\times$ 184 $mm^2$); 2) fluid-attenuated inversion recovery (FLAIR) (TR = 11 000 ms, TE = 120 ms, flip angle = $90^\circ$), 22 contiguous 5-mm-thick axial slices with a matrix size $= 512 \times 512$, FOV = $230 mm^2$); 3) 3D $T_1$-weighted fast field echo (TR = 25 ms, TE = 4.6 ms, flip angle = $30^\circ$), 220 contiguous axial slices with voxel size = 0.89 $\times$ 0.89 $\times$ 0.8 mm, matrix size = 256 $\times$ 256, FOV = 230 $\times$ 182 $mm^2$); and 4) pulsed-gradient SE echo planar with sensitivity encoding (acceleration factor = 2.5, TR = 8986 ms, TE = 80 ms, 55 contiguous 2.5-mm-thick axial slices, number of acquisitions = 2; after SENSE reconstruction, the matrix dimension of each slice was 256 $\times$ 256, with an in-plane pixel size of 0.94 $\times$ 0.94 mm and a FOV = 240 $\times$ 240 $mm^2$) and with diffusion gradients applied in 32 noncollinear directions using a gradient scheme which is standard on this system (gradient over-plus) and optimized to reduce echo time as much as possible. The b factor used was 1000 $s/mm^2$. Fat saturation was performed to avoid chemical shift artifacts. All slices were positioned to run parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum (CC).

**MRI Analysis**

WM hyperintensities (WMHs), if any, were identified on $T_2$ and FLAIR scans. WMH load was measured using the JIM5 software (Version 4.0, http://www.xinapse.com/Manual/index.html).

**WM Damage: TBSS and WM Tract of Interest Measurements**

DT MRI analysis was performed using the FMRIB software library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html) and the JIM5 software. Using FMRIB’s Linear Image Registration Tool (FLIRT), the 2 diffusion-weighted scans were coregistered by applying the rigid transformation needed to correct for position between the 2 $b_0$ images ($T_2$-weighted but not diffusion weighted). The rotation component was also applied to diffusion-weighted directions. Eddy currents correction was performed using the JIM5 software. Then, the 2 acquisitions were concatenated. The DT was estimated on a voxel-by-voxel basis using DTフィルタ provided by the FMRIB Diffusion Toolbox. Maps of mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (axD), and radial diffusivity (rAD) were obtained. TBSS version 1.2 (http://www.fmrib.ox.ac.uk/fsl/tbss/index.html) was used to perform the

### Table 1

Demographic and clinical data from healthy controls and patients

<table>
<thead>
<tr>
<th>N</th>
<th>HCbvFTD</th>
<th>bvFTD</th>
<th>P&lt;sub&gt;a&lt;/sub&gt;</th>
<th>HCPPA</th>
<th>P&lt;sub&gt;b&lt;/sub&gt;</th>
<th>PPA</th>
<th>P&lt;sub&gt;c&lt;/sub&gt;</th>
<th>Nonfluent</th>
<th>Semantic</th>
<th>Logopenic</th>
<th>P&lt;sub&gt;d&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>13</td>
<td>27</td>
<td>20</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>64.2 ± 5.8</td>
<td>61.0 ± 7.5</td>
<td>0.33</td>
<td>68.9 ± 5.9</td>
<td>0.86</td>
<td>67.7 ± 5.1</td>
<td>71.5 ± 6.5</td>
<td>66.8 ± 6.4</td>
<td>0.51&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (males)</td>
<td>10 (40%)</td>
<td>4 (31%)</td>
<td>0.73</td>
<td>15 (58%)</td>
<td>0.90&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.7 (67%)</td>
<td>3 (43%)</td>
<td>1 (25%)</td>
<td>0.55&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3.8 ± 3.1</td>
<td>3.9 ± 2.3</td>
<td>3.2 ± 2.1</td>
<td>0.20 ± 0.7</td>
<td>0.20 ± 0.7</td>
<td>20.4 ± 8.6</td>
<td>19.5 ± 5.2</td>
<td>0.27</td>
<td>0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>WMH volume (mL)</td>
<td>0.98 ± 1.28</td>
<td>0.65 ± 1.41</td>
<td>1.11 ± 1.41</td>
<td>2.39 ± 2.42</td>
<td>0.20</td>
<td>3.03 ± 2.74</td>
<td>2.77 ± 2.48</td>
<td>0.44 ± 0.52</td>
<td>0.13&lt;sup&gt;a&lt;/sup&gt;</td>
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Note: Numbers are means ± standard deviations or numbers (%). CDR-SB, clinical dementia rating scale sum of boxes; MMSE, Mini-Mental State Examination.

<sup>a</sup>Mann-Whitney U test or Fisher’s Exact test comparing bvFTD patients versus HCbvFTD.

<sup>b</sup>Mann-Whitney U test or Fisher’s Exact test comparing PPA patients versus HCPPA.

<sup>c</sup>Kruskall-Wallis or Fisher’s Exact tests among HCPPA and PPA variants.

<sup>d</sup>Kruskall-Wallis test among PPA variants.

<sup>P</sup><sub>c</sub> < 0.05 in semantic patients versus nonfluent and logopenic patient groups.
multisubject DT MRI analysis (Smith et al. 2006). FA volumes were aligned to a target image using the following procedure: 1) a target image was selected automatically as the most representative FA image by the FMRIB’s Nonlinear Image Registration Tool (FNIRT); 2) the nonlinear transformation that mapped each subject’s FA to the target image was computed using FNIRT; 3) the target image was transformed affinely to the Montreal Neurological Institute (MNI) 152 standard space; and 4) the same transformation was used to align each subject’s FA to the standard space. A mean FA image was then created by averaging the aligned individual FA images and thinned to create an FA skeleton representing WM tracts common to all subjects (Smith et al. 2006). The FA skeleton was thresholded at 0.2 to exclude voxels with low FA values, which are likely to include GM or cerebrospinal fluid (CSF). Individual MD, FA, axD, and radD data were projected onto this common skeleton.

Two WM atlases within FSL (http://www.nitrc.org/proj/wfu_pickatlas/), the Johns Hopkins University WM tractography atlas and the ICBM-DTI WM labels atlas, guided the definitions of WM tracts of interest, which included the anterior and posterior CC, cingulum, uncinate fasciculus, inferior frontooccipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), parahippocampal tract, superior longitudinal fasciculus (SLF), corticospinal tract, and fornix. WM tracts of interest were overlaid onto the mean FA image and masked with the WM skeleton. Mean DT MRI metrics were derived for each WM tract bilaterally.

**Brain Atrophy: Voxel-Based Morphometry and GM ROI Volumes**

Voxel-based morphometry (VBM) was performed using SPM8 and the Diffeomorphic Anatomical Registration Exponentiated Lie Algebra (DARTEL) registration method (Ashburner 2007), as previously described (Canu et al. 2011). Briefly, 1) T1-weighted images were segmented (Ashburner and Friston 2005) to produce GM, WM, and CSF tissue probability maps in the MNI space; 2) tissue segmentations were averaged across participants and smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel to create customized prior probability maps; 3) original T1-weighted images were segmented a second time using the custom priors to obtain new segmentation and normalization parameters; 4) T1-weighted images were rigidly aligned (using the rigid body component of the normalization parameters from step 3), segmented into GM and WM (using the segmentation parameters from step 3), and resampled to 1.5-mm isotropic voxels; 5) GM and WM segments were simultaneously coregistered using DARTEL; 6) the flow fields were then applied to the rigidly aligned segments to warp them to the common DARTEL space and then modulated using the Jacobian determinants. Since the DARTEL process warps to a common space that is smaller than the MNI space, we performed an additional transformation as follows: 7) the modulated images from DARTEL were normalized to the MNI template using an affine transformation estimated from the DARTEL GM template and the a priori GM probability map without resampling (http://brainmap.wisc.edu/normalizedDARTELtoMNI). Prior to the statistical computations, the images were smoothed with an 8-mm FWHM Gaussian filter.

GM ROIs were defined a priori between those connected by the WM tracts studied, using the WFU Pickatlas (http://www.nitrc.org/project/wfu_pickatlas/) in SPM8. Selected GM ROIs were: anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), inferior frontal and premotor cortices (including Brodmann areas 6 [premotor cortex], 44 [pars opercularis of the inferior frontal gyrus], and 45 [pars triangularis of the inferior frontal gyrus]), inferior parietal lobule, middle and superior temporal gyr, temporal pole, occipital cortex, and orbitofrontal cortex. GM ROI volumes were measured using the “Volumes” toolbox of SPM (http://sourceforge.net/projects/spmtools).

**Statistical Analysis**

**Demographic and Clinical Features**

Demographic and clinical variables were compared between groups using the Fisher’s Exact test for categorical variables and the Mann-Whitney U test or the Kruskal-Wallis test for continuous variables. A P value < 0.05 was considered as significant. Statistical analysis was performed using SAS Release 9.1 (SAS Institute, Cary, NC).

**WM Damage: Voxelwise Analysis**

DT MRI voxelwise statistics were performed using a permutation-based inference tool for nonparametric statistical thresholding (“randomize,” part of FSL; Nichols and Holmes 2002). The following contrasts were tested: bvFTD patients versus HCbwFTD and each PPA variant versus HCbwFTD, MD, FA, axD, and radD values within the skeleton were tested between groups using 2-sample t-tests adjusted for subject’s age. The number of permutations was set at 5000 (Nichols and Holmes 2002). The resulting statistical maps were thresholded at P < 0.05, corrected for multiple comparisons (familywise error, FWE) at the cluster level using the threshold-free cluster enhancement option in the randomize permutation-testing tool (Smith and Nichols 2009). For those contrasts that did not survive the correction for multiple comparisons, results were assessed at an uncorrected statistical level (P < 0.05).

**WM Damage: WM Tract of Interest Measurements**

For each DT MRI metric, comparisons between patients and controls were performed using linear mixed-effect model analysis (McCulloch et al. 2008), adjusted for subject’s age. Specifically, these models contained predictors for Group, Tract, and the Tract x Group interaction. Random intercepts were estimated to account for correlation among measures derived from the same subjects. The coefficients of Group and the Tract x Group interaction assess the tract-specific group differences for each DT MRI variable studied. Following the Wald’s approach, we tested if these coefficients were all zero, providing an overall multivariate test of the hypothesis that the group-specific means of a given variable were the same for each tract. If this hypothesis was rejected at α = 0.05, then tract-specific differences for each DT MRI variable were assessed using the Fisher’s Least Significant Difference Test. If we did not reject the null hypothesis of the multivariate test, we did not proceed to the second stage of this analysis. Results are reported as estimated means along with their standard errors. This analysis was performed using SAS Release 9.1.

A random forest approach was used (Breiman 2001) to model the relationship between the dichotomous outcome “subject status” (i.e., patient group vs. healthy controls and patient group vs. each other) and multiple potential predictor variables (i.e., DT MRI metrics), providing information on variable importance. The following comparisons were tested: bvFTD, nonfluent, and semantic versus controls and bvFTD, nonfluent, and semantic versus each other. The small number of logepenic patients did not allow us to perform such an analysis in this group. According to the random forest technique (Breiman 2001), 100 000 trees were built. The training set used to grow each tree is a 0.632+ bootstrap resample of the observations (Efron and Tibshirani 1993). The best split at each node was selected from a random subset of covariates (i.e., DT MRI metrics). The left-out observations (i.e., “out of bag” observations) were then predicted to obtain the classification error of the considered tree. The goodness of the fit of the random forest was assessed averaging the individual tree classification errors. Furthermore, the random forest framework estimates the importance of a predictor by looking at how much the classification error increases when out of bag data for that variable are permuted, while all others are left unchanged. The variables’ importance was ranked by assigning to each covariate a score based on the ability to predict correctly the dependent variable (i.e., patient group vs. healthy controls and patient group vs. each other) according to the increase of classification error when values of that covariate in a node were permuted randomly. We followed the strategy of Strobl et al. (2007) to avoid possible biases in variable selection: Individual classification trees were built using subsampling without replacement and adopting a conditional permutation scheme to compute variable importance in term of mean decrease in accuracy (i.e., each covariate receives a score according to its ability to classify the dataset directly the patient according to the decrease of classification accuracy) (Strobl et al. 2008). For the random forest analysis, we used the package “randomForest” version 4.5 implemented in R.

For the first 5 most important DT MRI variables, as ranked by the random forest analysis, we estimated also the Concordance index (C index) using a logistic regression analysis, which quantifies the predictive ability of the considered DT MRI variable in distinguishing the patient group from the healthy control group and the other patient groups.
Brain Atrophy: VBM
Analyses of covariance were performed to assess GM and WM differences between patients and healthy controls. Age and total intracranial volume were included in the models as covariates. The statistical threshold was set at \( P < 0.05 \) corrected for multiple comparisons using FWE. Results were also tested at \( P < 0.001 \) uncorrected for multiple comparisons within at least 50 contiguous voxels.

Relationship between WM Damage and GM Atrophy
The correlations between MD and FA values of specific WM tracts and GM ROI volumes were estimated using linear regression models adjusted for subject's age, in bvFTD patients and in PPA patients together. The models also included the interaction term between GM ROI volumes and Group. Correlations were defined a priori on the basis of the anatomy of the structures analyzed. Cingulum MD and FA values were correlated with ACC and PCC GM volumes. MD and FA values of the SLF were correlated with GM volumes of the inferior frontal and premotor cortices, inferior parietal lobule, and middle and superior temporal gyr. Uncinate MD and FA values were correlated with GM volumes of the temporal pole and orbitofrontal cortex; inferior parietal lobule, and middle and superior temporal gyri. Uncinate MD and FA values were correlated with GM volumes of the temporal pole and orbitofrontal cortex; ILF metrics values with GM volumes of the temporal pole and occipital cortex; and IFOF metrics with GM volumes of the orbitofrontal and occipital cortices. A \( P \) value < 0.05 was considered as significant. Correlation analysis was performed using SAS Release 9.1.

Results

Demographic and Clinical Features
Table 1 shows the demographic and clinical data of healthy controls and patients. Supplementary Table 1 reports the neuropsychological scores.

WM Damage: Voxelwise Analysis
bvFTD patients versus HC, bvFDTD (Fig. 1) showed increased MD in the CC (with an anterior–posterior gradient), fornix, bilateral external capsules, and bilateral frontal and anterior temporal WM. Small regions of increased MD were also detected in the superior and inferior parietal WM bilaterally. No region of increased MD was found in the occipital WM, brainstorm, and cerebellum. In bvFTD patients, regions of decreased FA were bilateral and included most of the CC (with an anterior–posterior gradient), cingulum bundles, corona radiata, external and internal capsules, subcortical WM subjacent to frontal and parietal cortex, temporal and occipital WM, fornix, and cerebral and cerebellar peduncles. bvFTD patients also showed a widespread pattern of increased radD, which included those regions where FA was altered (with the exception of the cerebellum). AxD was increased in the CC (with a predominance in the anterior portion), bilateral orbital and dorsolateral frontal WM, fornix, and right corona radiata, external capsule, and anterior temporal WM.

Nonfluent patients versus HC, bvFDTD (Fig. 2A) showed increased MD in the CC (with an anterior–posterior gradient), left cingulum, external capsule, corona radiata (with left predominance), and left orbitofrontal and temporal WM. In nonfluent patients, decreased FA was found in the CC (with a predominance in the anterior portion), cingulum, and fornix bilaterally. In the corona radiata, orbital, inferior and dorsolateral frontal WM, external capsule, and temporal and occipital WM, FA decreased predominantly in the left hemisphere. Small regions of decreased FA were also found in the cerebral peduncles. RadD was increased in those regions where FA was altered (with the exception of the occipital WM). AxD was increased in the left inferior and dorsolateral frontal WM and left inferior parietal WM.

The patterns of increased MD, radD, and axD in the semantic group versus HC, bvFDTD (Fig. 2B) were widespread and bilateral, involving most of the CC, cingulum, corona radiata, external and internal capsules, and orbitofrontal and temporal WM bilaterally, with a sparing of the occipital WM, brainstorm, and cerebellum. Semantic patients showed a decreased FA in the anterior CC, corona radiata (with left predominance), left external capsule, orbitofrontal WM (with left predominance), left dorsolateral frontal WM, and bilateral anterior temporal WM.

At a \( P < 0.05 \) FWE, no DT MRI difference was found between logopenic patients and HC, PPA. At \( P < 0.05 \) uncorrected logopenic patients showed (Fig. 2C): increased MD in the CC and left external capsule, anterior temporal WM, orbital and dorsolateral frontal WM, and inferior parietal WM; increased radD in the anterior CC (with left predominance), left cingulum, left orbital and dorsolateral frontal WM, left inferior parietal WM, and small regions in the left temporal WM; and increased axD in most of the CC, left cingulum, fornix, left temporal and inferior parietal WM, and small regions in the inferior and dorsolateral frontal WM. Decreased FA was found in the left anterior CC, left anterior and posterior cingulum, corona radiata (with left predominance), left external capsule, bilateral orbitofrontal and left inferior frontal WM, left temporal WM, and left inferior parietal WM.

WM Damage: Tract of Interest Measurements
Supplementary Tables 2 and 3 show the estimated means of the DT MRI metrics from the WM tracts studied as well as between group comparisons.

Table 2 shows the results of the random forest analysis in bvFTD, nonfluent, and semantic patients. For each comparison, the first 5 DT MRI variables in terms of importance in predicting correctly whether each individual belonged to a group or the other as well as their mean decrease in accuracy and C index are provided. The ranking of variable importance showed that, for all patient groups versus controls, left uncinate DT MRI measures provide the highest patient classification accuracy. The second most important predictors of patients versus controls were DT MRI metrics of the anterior CC in bvFTD, the left SLF in nonfluent, and the left ILF in semantic. All variables were able to classify correctly patients versus controls with a C index greater than 0.80 (i.e., more than 80% of patients were classified correctly using an individual variable). When patient groups were contrasted to each other, the left SLF and anterior CC measures provided the highest accuracy in distinguishing bvFTD from nonfluent cases (i.e., more severe left SLF damage in nonfluent vs. bvFTD, and more severe anterior CC damage in bvFTD vs. nonfluent; C index > 0.70). The most important predictors when bvFTD patients were compared with the semantic group were DT MRI variables of the left ILF and uncinate fasciculus (i.e., more severe left ILF damage in semantic vs. bvFTD, and more severe left uncinate damage in bvFTD vs. semantic; C index > 0.85). Finally, the ranking of variable importance showed that, for nonfluent versus semantic patients, left uncinate and ILF DT MRI measures resulted in the highest patient classification accuracy (i.e., more severe damage in semantic vs. nonfluent; C index > 0.85).
Brain Atrophy
Supplementary Tables 4–7 and Supplementary Figure 1 show VBM results. The regional distribution of tissue loss in each patient group was consistent with that reported in the literature (Mummery et al. 2000; Rosen et al. 2002; Gorno-Tempini et al. 2008).

Relationship between WM Damage and GM Atrophy
Figure 3 shows regions of GM atrophy and WM abnormalities in each patient group overlaid onto a common reference image. Supplementary Table 8 shows the results of the correlation analysis of WM tract MD and FA values with GM ROI volumes. bvFTD patients showed correlations between: the right SLF DT MRI metrics and volumes of the right middle and superior temporal gyri and inferior parietal lobule; the right ILF DT MRI metrics and volumes of occipital and temporal cortices and the left ILF MD and temporal pole volume; the IFOF DT MRI metrics and the orbitofrontal cortex volumes bilaterally; and the uncinate DT MRI metrics and volumes of the orbitofrontal and temporal cortices bilaterally. In the PPA group, correlations were found between the uncinate DT MRI metrics and temporal pole volumes bilaterally and between the left ILF MD and the left temporal pole volume.

Discussion
This study provides insights into the similarities and differences of the spatial patterns of WM damage in bvFTD and the 3 PPA variants. In each syndrome, albeit WM abnormalities that mirrored the distribution of GM atrophy, DT MRI changes extended well beyond the topography of GM loss. We propose a framework where DT MRI changes in FTLD-related syndromes are likely to offer additional biomarker of the disease, which may be useful in the diagnostic work up of these patients.

The strengths of our report compared with previous DT MRI studies of FTLD (Borroni et al. 2007; Matsuo et al. 2008; Agosta et al. 2010; Galanucci et al. 2011; Whitwell et al. 2011) are the following: 1) both bvFTD and PPA patients are included; 2) this is the first study to apply a nonaprioristic approach to quantify WM regional damage in patients with the 3 PPA variants, since in previous ones, the analysis was restricted to ROI (Matsuo et al. 2008; Agosta et al. 2010; Galanucci et al. 2011); 3) individual eigenvalues are used along with MD and FA to assess WM damage; 4) for the first time, a sophisticated statistical analysis is applied to measure the ability of DT MRI metrics in predicting each FTLD syndrome diagnosis; and 5) unlike most previous studies in FTLD, our study explicitly investigates GM/WM damage correlations.

Patients with bvFTD showed a widespread pattern of diffusivity and FA abnormalities affecting most of the WM bilaterally. DT MRI alterations were observed in WM tracts located in the frontal lobes, such as the anterior CC, cingulum, and SLF and in those passing through the temporal lobes, such as the uncinate, ILF, and IFOF. Along with frontotemporal GM atrophy, damage to both ventral and dorsal frontotemporal networks are likely to be responsible for the development of the typical behavioral symptoms of bvFTD. In agreement with previous studies (Borroni et al. 2007; Zhang et al. 2009; Whitwell et al. 2011), however, DT MRI alterations in this group were much more diffuse than the focal frontotemporal
atrophy. DT MRI abnormalities also include posterior brain regions, such as posterior CC and parietal and occipital WM. There are at least 2 possible explanations, which are not mutually exclusive, for this finding. First, although bvFTD is typically associated with frontal and anterior temporal atrophy (Rosen et al. 2002), patterns of atrophy are known to be

Figure 2. TBSS results in the variants of PPA compared with age-matched healthy controls: (A) nonfluent/agrammatic variant, (B) semantic variant, and (C) logopenic variant. Voxelwise group differences are shown in blue (MD), green (radD), cyan (axD), and red (FA). Results are overlaid on the coronal, sagittal, and axial sections of the MNI standard brain in neurological convention (right is right) and displayed at $P < 0.05$ corrected for multiple comparisons (family-wise error) for the nonfluent/agrammatic and semantic variants and at $P < 0.05$ uncorrected for the logopenic variant.
the involvement of frontoparietal WM tracts (Borroni et al. 2006). Indeed, previous studies of CBS and PSP have reported (CBS) or progressive supranuclear palsy (PSP) (Josephs et al. 2010). Many patients with the nonfluent variant may also progress to a syndrome compatible with corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (Josephs et al. 2006). Indeed, previous studies of CBS and PSP have reported the involvement of frontoparietal WM tracts (Borroni et al.

heterogeneous in this condition (Whitwell et al. 2009). Accordingly, VBM results in our cohort suggest a predominant frontotemporal involvement, but we cannot exclude that patients with the temporofrontoparietal variant were included (Whitwell et al. 2009). Second, even in the classic frontotemporal cases, the lateral and the medial parietal lobes usually become affected later in the disease course (Brambati et al. 2007). It is therefore tempting to speculate that DT MRI metrics may be viewed as early markers of WM integrity loss, which may result at a later stage in detectable volumetric abnormalities.

The left orbitofrontal, inferior frontal, anterior temporal, and inferior parietal WM regions were the most severely damaged in nonfluent patients. Abnormalities in these regions, which likely coincide with the uncinate and SLF, have been reported in previous studies (Galantucci et al. 2011; Whitwell et al. 2011). These results fit with the observation that the regions most severely atrophied in nonfluent patients were located in the left frontotemporal lobes and suggest that damage to the left frontotemporal–parietal network plays a role in the language deficits of these patients. In nonfluent patients, disease progression is associated with increasing difficulties with speech repetition and often the emergence of non-language symptoms, such as limb apraxia and dyscalculia, consistent with the involvement of the left posterior temporal and parietal lobes (Gorno-Tempini et al. 2004; Rohrer et al. 2010). Many patients with the nonfluent variant may also progress to a syndrome compatible with corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) (Josephs et al. 2006). Indeed, previous studies of CBS and PSP have reported the involvement of frontoparietal WM tracts (Borroni et al.

<table>
<thead>
<tr>
<th>Group comparison</th>
<th>Ranking of variable importance</th>
<th>Mean decrease in accuracy</th>
<th>C index</th>
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<tr>
<td>bvFTD versus controls</td>
<td>L uncinate radD</td>
<td>1.00</td>
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<td></td>
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Note: For each variable, mean decreases in accuracy as well as the C index obtained by the logistic regression analysis, are shown (for further details, see text). L — left.

Figure 3. Results of TBSS and VBM analyses are overlaid onto a common reference image (i.e., coronal, sagittal, and axial sections of the MNI standard brain) to show the anatomical localization of WM FA changes (dark green) and GM atrophy (yellow) in patients with bvFTD and each PPA variant. Results are shown in neurological convention (right is right) and displayed at the threshold specified in text. 2008; Erbetta et al. 2009). Whether the involvement of this frontotoparietal network is related to motor speech deficits in the nonfluent variant warrants further investigation.

The voxel-based analysis in the semantic group showed a focal asymmetrical pattern of FA abnormalities involving the anterior and inferior temporal WM and the inferior frontal and orbitofrontal regions, with a marked left predominance. These findings are in line with previous DT MRI studies (Borroni et al. 2007; Matsuo et al. 2008; Agosta et al. 2010; Galantucci et al. 2011; Whitwell et al. 2011) and mirrored the VBM results. On the contrary, when diffusivity alterations were investigated, semantic patients showed a widespread and bilateral pattern of damage including most of the ventral and dorsal frontal and temporal regions, spreading to the inferior parietal WM. Considering that mean disease duration in our cohort was about 5 years, this finding is not surprising. Indeed, disease progression in semantic patients is associated with diffuse left hemisphere damage and increasing involvement of the right frontotemporal regions (Brambati et al. 2009). As in the other groups, WM diffusivity abnormalities may precede atrophy.

Structural and DT MRI results in logopenic patients showed a pattern of damage involving the left inferior frontal cortex and temporoparietal junction as well as the frontotoparietal dorsal network and a few small regions in the CC and temporal lobe. The frontotoparietal WM is likely to represent part of the SLF. Such a pattern of damage is compatible with the sentence repetition and phonological short-term memory deficits of these patients (Gorno-Tempini et al. 2008). To date, only one study investigated DT MRI alterations in 9 patients with...
logopenic PPA using a tractography approach and showed that they had a severe involvement of the left SLF, in particular of its temporoparietal component (Galantucci et al. 2011). Although we included only 4 logopenic patients and, therefore, our results must be interpreted with caution, our study represents a step forward because it investigated the full extent of WM changes with no a priori assumptions about the spatial location of the tracts involved.

DT MRI findings in bvFTD and PPA patients are most likely due to axonal degeneration associated with injury/death of neuronal cell bodies. Consistent with this hypothesis, we found strong and anatomically congruent correlations between WM changes and regional GM atrophy in bvFTD and PPA patients. However, DT MRI findings may also reflect tau (Schofield et al. 2003) or TDP-43 (Neumann et al. 2007) deposition in the WM of the affected brain regions. That this may be an additional substrate of the observed abnormalities is supported by the fact that DT MRI alterations were also identified in WM not directly linked to atrophied GM regions. The assessment of regional alterations of raD and axD (Pierpaoli et al. 2001) can shed light into the complex structural abnormalities underlying DT MRI findings in our patients. In agreement with histopathological findings of myelin loss and pathologic accumulation in the oligodendrocytes of FTLD patients (Schofield et al. 2003; Neumann et al. 2007), we speculate that the increased raD we detected in most of the affected WM regions from bvFTD and PPA patients could reflect processes of demyelination (Pierpaoli et al. 2001). In contrast, axD changes, which are likely to be related to axonal damage (Pierpaoli et al. 2001), were more heterogeneous among groups, being as altered as raD in the semantic but less distributed in the bvFTD and nonfluent. Radiopathological correlations are more difficult to be interpreted in the logopenic group due to the small sample. In logopenic patients, axD abnormalities were more distributed than those of raD. Such a finding is intriguing when considering that a recent study showed MD and axD to be more widespread than raD in AD patients (Agosta et al. 2011), and since it has been suggested that the logopenic variant may be viewed as a left-lateralized form of AD (Migliaccio et al. 2009). Clearly, the biological interpretation of the relationships between WM and GM findings is challenging. First of all because this is a cross-sectional study, which cannot fully address the temporal sequence or causal relations between WM and GM abnormalities in FTLD. Longitudinal studies, with larger patient samples, are needed to define the temporal dynamics of WM and GM changes in bvFTD and PPA, which would contribute in the understanding of these diseases. Furthermore, TBSS and VBM approaches differ in many ways, including the way they are analyzed statistically, and this might influence, at least partially, the results. Despite these limitations, this study suggests that WM tract damage in FTLD is likely to occur, at least partially, independent of GM atrophy and that DT MRI is sensitive to such a damage.

Since voxel-based analysis showed that both bvFTD and PPA groups feature widespread patterns of WM damage, we questioned whether mean values of DT MRI metrics from critical WM tracts might differentiate better each syndrome from controls and each other. The variables that showed to be the most important predictor of FTLD (of any type) versus controls were those reflecting a damage to the left uncinate, which were able to classify correctly about 90% of patients in each group versus controls, with the highest classification accuracy in semantic patients (99%). Uncinate damage is one of the most consistent DT MRI abnormalities reported in the available literature in bvFTD (Matsuo et al. 2008; Zhang et al. 2009; Whitwell et al. 2011), semantic (Agosta et al. 2010; Whitwell et al. 2011), and nonfluent (Whitwell et al. 2011) patients. Given its anatomical distribution, uncinate injury is likely to be responsible for the behavioral symptoms, which are shared by all FTLD syndromes (Rohrer and Warren 2010). An association between orbitofrontal damage and behavioral symptoms has been shown in bvFTD (Borroni et al. 2007) and PPA (Rohrer and Warren 2010). Although it has been suggested that the uncinate is part of a circuitry involved in semantic memory and name retrieval (Papagno et al. 2011), its role in language processing is still debated. In addition, the random forest approach identified group-specific WM tracts with a good discriminative capability in each syndrome versus the others. The role of anterior CC damage in bvFTD patients is in line with their predominant frontal clinical and neuropathological involvement (Borroni et al. 2007; Matsuo et al. 2008; Zhang et al. 2009; Whitwell et al. 2011). Our findings also confirmed that the nonfluent variant is associated with a severe injury of the dorsal language network (Whitwell et al. 2011), which can be useful to differentiate nonfluent from bvFTD cases. The severe ILF damage was found to contribute to language impairment in semantic patients (Borroni et al. 2007; Matsuo et al. 2008; Agosta et al. 2010; Whitwell et al. 2011) and differentiate them from those patients with other FTLD syndromes with a high classification accuracy. Although our approach needs to be replicated in independent clinical data sets and validated in pathologically verified patient samples, our findings suggest that DT MRI may be a useful biomarker to help in distinguishing each syndrome from cognitively normal individuals and patients with other FTLD syndromes. Furthermore, since the involvement of the uncinate is a well-known feature also in AD (Zhang et al. 2009), the contribution to a reliable discrimination of FTLD syndromes from AD needs to be tested. Nevertheless, it is worth noting that an improved reliability in diagnosing and monitoring FTLD variants using DT MRI may be increasingly important as disease-specific modifying treatments will become available.

**Supplementary Material**

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

**Notes**

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**Conflict of Interest**: None declared.

**References**


