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# Longitudinal white matter changes in frontotemporal dementia subtypes

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**Abstract**

Frontotemporal lobe dementia is a degenerative brain condition characterised by focal atrophy affecting the frontal and temporal lobes predominantly. Changes in white matter with disease progression and their relationship to grey matter atrophy remain unknown in FTD. This study aimed to establish longitudinal white matter changes and compare these changes to regional grey matter atrophy in the main FTD subtypes

Diffusion and T1-weighted images were collected from patients with behavioural-variant FTD (bvFTD: 12), progressive nonfluent aphasia (PNFA: 10), semantic dementia (SD: 11) , and 15 controls12 months apart. Changes in white matter integrity were established using fractional anisotropy, mean, axial and radial diffusivity measurements and patterns of cortical grey matter atrophy were measured using voxel-based morphometry.

At baseline, bvFTD showed severe white matter changes in orbitofrontal and anterior temporal tracts, which progressed to involve posterior temporal and occipital white matter. In PNFA, initial degeneration occurred bilaterally in frontotemporal white matter (left > right), with subsequent changes more prominent on the right. Initial white matter changes in SD were circumscribed to the left temporal lobe, with subsequent changes extending to bilateral frontotemporal tracts. In contrast, progression of grey matter change over time was less pronounced in all FTD subtypes. Mean diffusivity was most sensitive in detecting baseline changes while fractional anisotropy and radial diffusivity revealed greatest changes over time, possibly reflecting different underlying pathological processes with disease progression. Our results indicate that investigations of white matter changes appear to be a sensitive approach to detect disease progression in FTD subtypes.

## Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disease, affecting the frontal and temporal lobes predominantly. It is characterised by three main clinical phenotypes (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). The behavioural-variant of FTD (bvFTD) is the most common clinical phenotype and is typified by early changes in personal, social, interpersonal conduct and loss of insight (Piguet et al., 2011). On magnetic resonance imaging (MRI), bvFTD is associated with bilateral frontal and anterior temporal grey matter atrophy (Boccardi et al., 2005; Rosen et al., 2002; Seeley et al., 2008). The remaining patients present with predominant language deficits, which can be either fluent (semantic dementia; SD) or nonfluent (progressive nonfluent aphasia; PNFA). SD is characterised by a progressive loss of semantic or world knowledge. The language output remains fluent but empty with a reduction of expressive vocabulary but intact grammar and phonology (Gorno-Tempini et al., 2004; Hodges et al., 1992). Brain imaging is characteristic with profound asymmetric anterior temporal lobe atrophy, generally more pronounced on the left (Hodges and Patterson, 2007; Kipps et al., 2007). Patients with PNFA present with hesitant distorted speech and/or agrammatism (Gorno-Tempini et al., 2004; Grossman et al., 1996). This presentation is associated with atrophy of the left posterior fronto-insular region (Gorno-Tempini et al., 2004). As the disease progresses, clinical features tend to merge across clinical phenotypes and brain atrophy becomes more extensive with bilateral involvement (Rosen et al., 2002; Whitwell et al., 2004).

Advances in diffusion tensor imaging (DTI) techniques in recent years have led to a number of investigations on white matter integrity in FTD subtypes (Acosta-Cabronero et al., 2011; Agosta et al., 2010; Agosta et al., 2011; Borroni et al., 2007; Galantucci et al., 2011; Mahoney et al., 2012; Matsuo et al., 2008; Schwindt et al., 2011; Whitwell et al., 2010; Zhang et al., 2009; Zhang et al., 2013). Importantly, significant differences in regional

severity occur depending on the DTI metrics used. Further, cross-sectional studies show that the extent of white matter damage cannot be predicted by the degree of associated grey matter atrophy (Agosta et al., 2011; Mahoney et al., 2012; Schwindt et al., 2011). The question of whether there is a tight coupling of the white and grey matter damage over time and with disease stage or type remains unknown. This study aimed to establish the regional pattern and severity of white matter damage in the different FTD syndromes over 12 months, and to compare the progression of white matter change to grey matter change over the same time period.

## Materials and methods

***Participant recruitment*** – Thirty-three individuals diagnosed with FTD (bvFTD = 12; PNFA = 10; SD = 11) were recruited from the Frontier research clinic at Neuroscience Research Australia (NeuRA), Sydney, Australia into this study. All patients were seen by the same experienced neurologist (JRH) and met current clinical diagnostic criteria for FTD (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). Patients with logopenic progressive aphasia were excluded from this study. In addition, 15 age- and sex-matched healthy controls were recruited from the NeuRA brain donor program and from local community clubs. Healthy controls scored 0 on the Clinical Dementia Rating (Morris, 1993) and above 88/100 on the Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi et al., 2006). Exclusion criteria included prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease, alcohol and other drug abuse, use of psychotropic medication, and limited English proficiency. Because MRI uses high-field magnets in a confined environment, individuals with ferromagnetic implants or a prior history of claustrophobia were also excluded.

Ethical approval for this study was obtained from the Southern Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

***Image acquisition*** **-** Whole-brain diffusion-weighted and T1 images were obtained from a 3-Tesla scanner (Philips Achieva 3.0T TX) with a standard 8-channel head coil. For the diffusion-weighted sequence, two sets of whole-brain echo-planar images were acquired with 32 non-collinear gradient directions (repetition time /echo time /inversion time: 8400 /68 /90 ms; b-value = 1000 s/mm$^2$; 55 slices, horizontal slice thickness 2.5 mm, end resolution: 2.5 x 2.5 x 2.5 mm$^3$; field of view: 240 x 240 mm, 96 x 96 matrix). Two sets of 3D T1-weighted images were also acquired in the coronal plane (echo time/ repetition time: 2.6/5.8ms, 200 slices, slice thickness 1 mm, in-plane resolution: 1 X 1 mm$^2$, in-plane matrix: 256 x 256). All images were visually inspected for quality and images with a large degree of head movement or with obvious white matter hyperintensities were excluded. One PNFA subject was excluded for VBM analysis due to issues with the acquired T1 image, but was included in the DTI analysis, as detailed below.

***Tract-based spatial statistics*** **-** DTI data were processed with Tract-based spatial statistics (TBSS v 1.2) (Smith et al., 2006), part of the Functional MRI of the Brain Software Library (FSL v 4.1.9) (Smith et al., 2004). The two DTI sequences were averaged to improve signal-to-noise ratio before being corrected for eddy current distortions and head movements using affine registration to the non-diffusion volumes (b0). Then, the Brain Extraction Tool was applied to both the b0 images and the diffusion-weighted images (Smith, 2002). Each brain was visually checked to ensure the accurate removal of all non-brain tissues during the skull-stripping process. Finally, a tensor model was fitted into the diffusion images using FMRIB Diffusion Toolbox, and the primary, secondary and tertiary tensor eigenvalues ($\lambda_1$, $\lambda_2$ & $\lambda_3$)

were generated (Smith et al., 2004). The four DTI metrics obtained included axial diffusivity (AxialD), which is the diffusion coefficient along the main axis; radial diffusivity (RadialD), the averaged diffusion coefficient along the perpendicular axes; mean diffusivity (MD), the averaged diffusion coefficient along all axes; and fractional anisotropy (FA), which is the ratio of the above metrics, generating a value between 0 to 1 to show the overall magnitude and orientation of water diffusion in tissue.

In order to perform voxelwise multi-subject analyses of DTI data between controls and baseline scans, each individual FA map was transformed to the FMRIB58 fractional anisotropy template obtained from the FSL software and then affine-registered into the Montreal Neurological Institute standard space (MNI-152) using the FSL nonlinear registration tool (FNIRT) (Andersson et al., 2007a; Andersson et al., 2007b). Following image registration, the averaged FA data were thinned to create a skeleton of white matter that signified the centers of all white matter tracts (lines of maximum FA) common to the group. Then, each individual FA data point was projected on the mean FA skeleton to correct residual misalignment and to line up the centers of individual tracts. The mean FA skeleton was thresholded at 0.2 to minimize partial volume effects and inter-subject variability. AxialD, RadialD and MD data were also mapped onto the skeleton using projection vectors from the FA-to-skeleton transformation for each individual (Smith et al., 2006). The same protocol was used to perform voxelwise multi-subject analyses between baseline and follow-up scans.

***Voxel-based morphometry*** –Voxel-based morphometry (VBM) from the FSL suite was used to perform grey matter analysis (Ashburner and Friston, 2000; Good et al., 2001). T1-weighted images underwent the Brain Extraction Tool to remove any non-brain matter (Smith, 2002) and the brain was segmented into grey, white matter and cerebrospinal fluid using FMRIB's Automatic Segmentation Tool (Zhang et al., 2001). The images were then

registered into the MNI-152 standard space using non-linear registration (Andersson et al., 2007a; Andersson et al., 2007b). The space-transformed images were averaged and flipped along the x-axis to produce a symmetric, study-specific grey matter template. All native T1 scans were non-linearly registered to the study-specific template for modulation (to correct for local expansion or contraction due to non-linear component of the spatial transformation). The resulting images were averaged and flipped along the x-axis to produce a left-right symmetric, study-specific grey matter template and were smoothed with an isotropic Gaussian kernel with a sigma of 3mm (full width half maximum = 8mm).

***Voxelwise statistical analysis*** – In TBSS, a voxel-wise general linear model was applied and clusters were generated from a permutation-based (5000 permutations performed), non-parametric test with the threshold-free cluster enhancement option. Cross-sectional contrasts between each FTD group and controls were examined first followed by longitudinal contrasts between baseline and follow-up scans within each FTD group. Masks of white matter tracts were generated for the extraction of DTI metrics. White matter locations of significant clusters were determined by reference to the John Hopkins University white matter atlas and the ICBM-DTI-WM atlas labels integrated into FSLview (Mori et al., 2008; Oishi et al., 2008). Grey matter locations of significant clusters were determined by reference to the MNI structural atlas and Harvard-Oxford Cortical Structural Atlas. The statistical threshold was set at $p < 0.05$ corrected for multiple comparisons (family-wise error) for all analyses. Relationships between the locations of white and grey matter changes were examined by overlaying FA measurements to the grey matter VBM changes, in order to allow comparisons with previous investigations (Agosta et al., 2011; Mahoney et al., 2012; Schwindt et al., 2011; Zhang et al., 2013).

**Results**

***** Insert Table I about here *****

Demographic and clinical characteristics of study participants are presented in Table I. Groups were well matched for age, years of education and sex. Not surprisingly, a significant group difference was observed on the ACE-R, with all FTD groups scoring significantly lower than controls. In addition, SD patients scored significantly lower than the PNFA group on the ACE-R, reflecting the semantic loading of this instrument. Further, disease duration was significantly longer in SD compared with PNFA patients (Table I).

**Cross-sectional white matter changes in FTD subtypes**

Results from the DTI analyses showed the expected patterns of differential white matter changes at baseline in all the FTD subtypes (Figure 1) (Acosta-Cabronero et al., 2011; Agosta et al., 2011; Mahoney et al., 2012; Schwindt et al., 2011). Differences in the data, however, were observed in the FTD subtypes depending on the DTI metrics.

***** Insert Figure 1 about here *****

*Behavioural-variant FTD:* All DTI measures revealed significant bilateral changes (reduced FA and increased MD, AxialD and RadialD) in similar locations, most pronounced in frontotemporal regions, early in the bvFTD group compared to controls. The changes occurred in the anterior thalamic radiation, anterior cingulum, superior and inferior longitudinal, inferior frontal-occipital and uncinate fasciculi, as well as the genu of the corpus callosum. Abnormalities on MD and RadialD appeared the most extensive in this FTD subgroup (Figure 1).

*Progressive nonfluent aphasia:* In this group, early left greater than right white matter changes were observed in the superior and inferior longitudinal fasciculi, as well as in the

body and splenium of the corpus callosum. Abnormalities were generally more pronounced in the MD and RadialD DTI measures for this FTD group (Figure 1).

*Semantic Dementia:* Early white matter changes in SD were identified only in the left hemisphere (Figure 1). Regional white matter changes included the left cingulum, left superior and inferior longitudinal and uncinate fasciculi. Similarly located abnormalities were detected by all four DTI metrics, with most extensive changes found in MD and AxialD in this FTD subgroup.

**Relationship between early cross-sectional white matter changes and cortical atrophy**

Results from the VBM analyses showed the expected patterns of grey matter changes in all the FTD subtypes (Figure 2) (Agosta et al., 2011; Boccardi et al., 2005; Mummery et al., 2000; Pan et al., 2012). This analysis confirmed that abnormalities in the white matter extended beyond the sites of grey matter atrophy (Agosta et al., 2011; Mahoney et al., 2012; Schwindt et al., 2011). This discrepancy was most pronounced in the PNFA group, where grey matter atrophy occurred in the inferior frontal and insula regions with additional white matter changes found in the corpus callosum and parietal regions bilaterally. In bvFTD, where white matter changes extended into the posterior temporal and occipital regions, compared to the predominant reduction in grey matter of the frontal and anterior temporal lobes bilaterally. While grey matter atrophy was present in the anterior temporal regions bilaterally in SD, changes in white matter tracts were observed in the left hemisphere only (Figure 2).

***** Insert Figure 2 about here *****

**Longitudinal white matter changes in FTD subtypes**

*Behavioural-variant FTD:* At 12 months, extensive bilateral changes continued in most white matter tracts across all DTI metrics compared to baseline measurements but also including the splenium of the corpus callosum. Longitudinal changes in FA and RadialD were concordant with each other and showed the most extensive changes among all metrics (Supplementary Table I) with some tracts spared using other DTI measures (right anterior cingulum and left superior longitudinal fasciculus in MD; bilateral anterior cingulum, superior and inferior longitudinal fasciculi in AxialD) (Figure 3).

***** Insert Figure 3 about here *****

*Progressive nonfluent aphasia:* After 12 months, additional white matter abnormalities were observed in this group (anterior thalamic radiation, anterior cingulum, uncinate fasciculus and genu of corpus callosum), with the changes becoming more pronounced in the right compared to the left hemisphere (except for the anterior thalamic radiation which occurred on the left) (Figure 4). Longitudinal DTI changes were observed in FA, MD and RadialD only. Changes in AxialD were observed in the inferior-fronto-occipital fasciculus only when using a more liberal significance threshold ($p < .001$ uncorrected) (Supplementary Table II).

***** Insert Figure 4 about here *****

*Semantic dementia:* In contrast, progressive longitudinal white matter changes in the SD group extended into frontal (inferior-fronto-occipital fasciculus) and commissural tracts (splenium of the corpus callosum) at 12 months, with less progression in left temporal regions (no progression in cingulum) (Figure 5). Longitudinal alterations in FA were most extensive compared to the other metrics in SD, particularly in frontal white matter regions (Supplementary Table III). Longitudinal changes in AxialD were found in the left temporal region only at the $p < .001$ uncorrected for multiple comparisons.

***** Insert Figure 5 about here *****

**Longitudinal white and grey matter changes in FTD subtypes**

At the 12-month follow up, the progression of white matter abnormalities appeared more pronounced and widespread than the progression of grey matter atrophy in all FTD subtypes (Figure 6). In bvFTD, the progression of grey matter atrophy was localised to the right fronto-temporal region while progressive white matter abnormalities were observed bilaterally. In PNFA, only additional white matter changes were detected in the temporo-parieto-occipital regions bilaterally at 12 months. In contrast, no significant grey matter changes were found over the same time period. When using a more liberal significance threshold ($p < .001$ uncorrected for multiple comparisons), grey matter atrophy was observed in the left superior frontal and lateral occipital cortices bilaterally. In SD, while bilateral white matter changes were observed in frontotemporal regions, only circumscribed additional left hippocampal grey matter atrophy occurred over the same 12-month period (Figure 6, Supplementary Table IV).

***** Insert Figure 6 about here *****

**Discussion**

This study reports longitudinal white matter changes in FTD subtypes. Our findings demonstrate specific profiles of white matter changes in each FTD subtype over a 12-month period. Importantly, the location and severity of these changes varied depending on the DTI metrics used, indicating that white matter changes shown with different DTI measures may represent different pathological processes. Further, our investigations demonstrated that, over the course of 12 months, white matter abnormalities showed more extensive progression, compared to grey matter changes, over the same time period.

Our investigations revealed that most white matter changes identified at follow up co-localized with the distribution of white matter abnormalities uncovered at baseline in all FTD subtypes. Importantly, however, the tissue abnormalities progressed to involve similar regions in the other hemisphere, giving rise to a bilateral, rather than focal, pattern of white matter change with disease progression. This progression is particularly dramatic in bvFTD where the orbitofrontal and anterior temporal regions, which were most affected at baseline, continue to progress bilaterally at follow-up, with additional posterior involvement, such as that of the splenium of the corpus callosum. Notably, this profile of white matter change was observed regardless of the metric used, and indicates a particularly early and rapidly progressive pathological change. In contrast, the longitudinal white matter changes found in PNFA were not as dramatic as those observed in bvFTD. Changes in this group appeared to remain relatively focal, even with progression, with the pattern of change over time involving more distant tracts connected to the primary site of brain atrophy. Finally, in SD, longitudinal white matter changes became widespread affecting bilateral temporal regions. The widespread and rapidly progressive white matter changes over time in bvFTD are consistent with the shorter life expectancy (Garcin et al., 2009; Onyike, 2011) and faster cognitive decline (i.e., ACE-R or frontotemporal dementia rating scale) generally reported in these patients compared to the other FTD subtypes (Kipps et al., 2008; Piguet et al., 2011).

Our analyses also uncovered that the spatial relations between white and grey matter changes varied over time in all FTD subtypes. At baseline, changes in white matter integrity, as measured by DTI, mapped relatively closely to the reduction in grey matter measured by VBM. At 12 months, however, the rate and location of change in the white and grey matter became uncoupled. Atrophy of the grey matter atrophy progressed only minimally over that time period with the damage remained relatively focal. In contrast, white matter changes

became widespread with bilateral alterations in frontotemporal regions and the damage encroaching into the posterior white matter in all FTD subtypes.

Co-localisation of white and grey matter abnormalities in FTD have been reported in some studies (Acosta-Cabronero et al., 2011; Hornberger et al., 2010) but not others (Agosta et al.; Mahoney et al., 2012; Schwindt et al., 2011; Zhang et al., 2013). Some studies have suggested that white matter abnormalities are an early marker of FTD as opposed to the volumetric grey matter loss occurring later in the disease (Agosta et al.; Mahoney et al., 2012; Schwindt et al., 2011; Zhang et al., 2013). Our study confirms the extensive pathological changes in white matter in all subtypes of FTD, changes that tend to extend beyond those observed using cross-sectional or longitudinal measures of grey matter atrophy. Our findings reveal different temporal and spatial patterns of white and grey matter pathology over time in FTD. Direct comparisons of the longitudinal changes affecting the white and grey matter need to be approached with caution, given the different imaging modalities used to investigate these two types of tissue. Nevertheless, the magnitude of white matter change observed over 12 months using DTI indicates that this methodology is sensitive and appropriate to measure disease progression in FTD subtypes, regardless of the grey matter changes.

Previous investigations of white matter changes in FTD have generally used FA as a single marker of white matter change. The combination of different DTI metrics (RadialD, AxialD, MD), which measure different aspects of diffusion behaviour in the white matter, appears more sensitive in detecting white matter changes in neurodegenerative conditions rather than the use of a single global diffusion measure such as FA (Acosta-Cabronero et al., 2010). At baseline, MD and RadialD alterations were most severe in bvFTD and PNFA, while MD and AxialD abnormalities were most prominent in SD. At follow-up, however, FA and RadialD revealed the most prominent changes in the white matter tracts in all three subtypes of FTD.

These findings concord with those reported in Alzheimer's disease, where MD and AxialD were the first metrics to detect white matter alterations, while alterations in RadialD and FA became more pronounced with disease progression (Acosta-Cabronero et al., 2012). Together, these data support the view that DTI metrics identify different underlying processes specific to the stage of the disease. These findings are also likely to explain the variable co-localisation between white and grey matter changes reported above, given the single DTI measurement obtained in previous studies.

Animal studies have suggested that an increase in AxialD correlates with axonal degeneration while an increase in RadialD suggests myelin loss (Beaulieu, 2002; Song et al., 2002). Our findings suggest the combination of different DTI metrics across repeated MRIs may provide important biological cues about the underlying changes occurring in the different FTD subtypes over time. Human DTI data, however, require careful interpretation, given the greater structural heterogeneity using this indirect method compared with histopathological observations in animal models. Inclusion of grey matter, crossing fibres and residual misalignment may all cause changes to absolute diffusivities or eigenvalues which may not necessarily reflect underlying pathologies (Zhang et al., 2013). In addition, given the complexity of pathological changes affecting the white matter (altered myelination, neurodegeneration, gliosis, calcification, etc.) (Sierra et al., 2011), a single diffusion metric is unlikely to correlate best with a unique pathological process (Acosta-Cabronero et al., 2010; Mahoney et al., 2012; Pierpaoli et al., 2001). Further, unlike other dementia syndromes, the neuropathology of FTD is complex and remains often unpredictable in life. FTD subtypes share abnormal protein depositions of either tau (in bvFTD and PNFA), tar DNA binding protein 43 (in bvFTD and SD) or, in a small proportion, fused in sarcoma (in bvFTD) (Davies et al., 2005; Hodges et al., 2004; Josephs et al., 2006; Knibb et al., 2006; Lee et al., 2011; Mackenzie et al., 2010; Mesulam et al., 2008). The variability in protein deposition within

and across FTD subtypes likely contributes to the complexity in interpreting changes identified on diffusion-weighted images. Postmortem histopathological confirmation of the type of change being detected *in vivo* with DTI overtime will clarify whether the relationships reported in animal studies hold in humans (Beaulieu, 2002; Song et al., 2002).

Longitudinal imaging studies in FTD are much less common than cross-sectional investigations. Undoubtedly, longitudinal investigations present the challenge of obtaining data of good quality in patients prone to movements at two (or more) time points. The undeniable advantage of such designs, however, is that they avoid the issue of inter-subject variability. As study participants act as their own control, they provide reliable indices of changes over time as the disease progresses. In order to avoid bias in the registration and analyses of baseline and follow-up image, all images were aligned to the same target template within the FSL suite to ensure robust and unbiased registration (Smith et al., 2006). In addition, we used randomise, a permutation method within FSL, to reduce the risk of false positives (Thomas et al., 2009). This registration protocol was applied to all images.

## Conclusion

This study investigated longitudinal white matter and grey matter changes concurrently in FTD. The results highlight differential white matter changes at baseline and over a 12-month period in the three FTD subtypes. Our data show that these white matter changes extend beyond those observed in the grey matter during the same time period, indicating that imaging of the brain white matter is particularly sensitive to identifying the progression of pathology in FTD. In addition, the progression of white matter abnormalities differs depending on the DTI metrics used, suggesting that different metrics may detect different pathological processes occurring at different disease stages, although tissue validation of this concept is now required.

These findings have implication for clinical trials, particularly in bvFTD. The extensive involvement of the white matter pathology and its rapid progression over time, compared to grey matter atrophy, indicates that monitoring of these white matter changes may help establish the impact of therapeutic treatments in FTD syndromes over a relatively short time period.

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Table and Figure legends

Table I. Numerical values are illustrated in mean ± standard deviation. * denotes chi-square test. Significant differences were observed in ACE-R between all FTD subtypes (bvFTD, PNFA and SD) and controls ($p < 0.01$). ^ denotes significant differences between PNFA and SD. Abbreviations: M = male; F = female; NS = not significant. ACE-R = Addenbrooke's Cognitive Examination-Revised; yr = year; bvFTD = behavioural-variant frontotemporal dementia; PNFA= progressive nonfluent aphasia; SD = semantic dementia.

Figure 1. Cross-sectional WM changes in bvFTD, PNFA and SD compared to controls for the four DTI metrics (FA, MD, AxialD, RadialD). TBSS results of voxel-wise group differences are shown thresholded at $p < 0.05$, corrected for family-wise error for multiple comparisons. Results are overlaid on coronal sections of the MNI standard brain in radiological convention. L = left; R = right.

Figure 2. Cross-sectional changes in grey matter compared to controls overlaid on common reference MNI template. Reductions in grey matter density (in yellow) are illustrated for the bvFTD, PNFA and SD groups. Significant clusters were thresholded at $p <0.05$, corrected with family-wise error for multiple comparisons. Results are overlaid on sagittal, axial and coronal sections of the MNI standard brain in neurological convention. L = left; R = right.

Figure 3. TBSS results of longitudinal white matter changes in bvFTD. Voxel-wise group changes from baseline are shown for FA, MD, AxialD and RadialD ($p < 0.05$, corrected for family-wise error multiple comparisons). Results are overlaid on sagittal, axial and coronal sections of the MNI standard brain in radiological convention. L = left; R = right.

Figure 4. TBSS results of longitudinal white matter changes in PNFA. Voxel-wise group changes from baseline are shown for FA, MD and RadialD ($p <0.05$, corrected for family-

wise error multiple comparisons). No significant result was found in AxialD. Results are overlaid on sagittal, axial and coronal sections of the MNI standard brain in radiological convention. L = left; R = right.

Figure 5. TBSS results of longitudinal white matter changes in SD. Voxel-wise group changes from baseline are shown for FA, MD and RadialD ($p < 0.05$, corrected for family-wise error multiple comparisons). No significant result was found in AxialD. Results are overlaid on sagittal, axial and coronal sections of the MNI standard brain in radiological convention. L = left; R = right.

Figure 6. Longitudinal changes in grey matter and white matter in FTD subtypes. FA changes (in red) and grey matter atrophy (in yellow) over a 12-month period are illustrated for bvFTD, PNFA and SD. All analyses corrected for multiple comparisons at $p < .05$ for family-wise error. No significant grey matter cluster was observed in PNFA. Results are overlaid on sagittal, axial and coronal sections of the MNI standard brain in radiological convention. L = left; R = right.