Longitudinal White Matter Changes in Frontotemporal Dementia Subtypes

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Abstract: Frontotemporal dementia is a degenerative brain condition characterized 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 T_1 -weighted images were collected from behavioral-variant FTD (bvFTD: 12), progressive non-fluent aphasia (PNFA: 10), semantic dementia (SD: 11), and 15 controls at baseline and 12 months apart. Changes in white matter integrity were established by fractional anisotropy, mean, axial and radial diffusivity measurements using tract-based spatial statistics. Patterns of cortical grey matter atrophy were measured using voxel-based morphometry. At baseline, bvFTD showed severe cross-sectional changes in orbitofrontal and anterior temporal tracts, which progressed to involve posterior temporal and occipital white matter over the 12-month. In PNFA, cross-sectional changes occurred bilaterally in frontotemporal white matter (left > right), with longitudinal changes more prominent on the right. Initial white matter changes in SD were circumscribed to the left temporal lobe, with longitudinal 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 reveal important differences across FTD syndromes with disease progression. *Hum Brain Mapp* 35:3547–3557, 2014. © 2013 Wiley Periodicals, Inc.

Key words: frontotemporal dementia; longitudinal white matter changes; diffusion tensor imaging; tract-based spatial statistic; voxel-based morphometry

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INTRODUCTION

Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disease, affecting the frontal and temporal lobes predominantly. It is characterized by three main clinical phenotypes (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011). The behavioral-variant 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 non-fluent (progressive non-fluent aphasia; PNFA). SD is characterized by a progressive loss of semantic or world knowledge. The language output remains fluent with intact grammar and phonology but empty with a reduction of expressive vocabulary (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, 2011; Borroni et al., 2007; Galantucci et al., 2011; Mahoney et al., 2013; Matsuo et al., 2008; Schwindt et al., 2013; Whitwell et al., 2010; Zhang et al., 2009, 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., 2013; Schwindt et al., 2013). 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 each of the main FTD syndromes over 12 months, and compare the progression of white matter change to grey matter changes 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). Pathological confirmation of frontotemporal lobar degeneration was subsequently obtained for two patients. *Postmortem* investigations revealed one bvFTD patient to have TDP-43 protein inclusions while another patient, diagnosed with PNFA, showed tau positive inclusions, the distribution of which was consistent with a pathological diagnosis of progressive supranuclear palsy. 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 T_1 images were obtained from a 3-T scanner (Philips Achieva 3.0T TX) with a standard eight-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 = 1000s/mm²; 55 slices, horizontal slice thickness 2.5 mm, end resolution: $2.5 \times 2.5 \times 2.5$ mm³; field of view: 240×240 mm, 96×96 matrix). Two sets of 3D T_1 -weighted images were also acquired in the coronal plane (echo time/ repetition time: 2.6/5.8 ms, 200 slices, slice thickness 1 mm, in-plane resolution: 1×1 mm², in-plane matrix: 256×256). 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 T_1 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 1.1; Smith et al., 2006), part of the Functional

MRI of the Brain Software Library (FSL v 4.1.9; Smith et al., 2004). Image pre-processing involved the following steps. First, 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 (b_0). Then, the Brain Extraction Tool was applied to both the b_0 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 (λ_1 , λ_2 , and λ_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.

Then, imaging data were processed using the following methodology, which can be summarized in four steps. First, each individual FA map (baseline FTD and control) was transformed to the FMRIB58 fractional anisotropy template obtained from the FSL software using nonlinear registration. All aligned FA images were affine-registered into the Montreal Neurological Institute standard space (MNI-152; Andersson et al., 2007a, 2007b). Second, 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. Third, 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. Finally, 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 longitudinal imaging data was conducted in a separate analysis. FA maps from baseline and follow-up scans within each FTD subtype were registered non-linearly to the FMRIB58 fractional anisotropy standard template. The mean FA skeleton was derived from baseline and follow-up FA maps within each FTD subtype. Other processing steps were identical to the procedure described above. This method has been used previously in other longitudinal studies (Acosta-Cabronero et al., 2012; Barrick et al., 2010; Teipel et al., 2010; Weaver et al., 2009).

Voxel-Based Morphometry

Voxel-based morphometry (VBM) from the FSL suite was used to perform grey matter analysis (Ashburner and Fris-

ton, 2000; Good et al., 2001). T_1 -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, 2007b). The space-transformed images were averaged and flipped along the x -axis to produce a symmetric, study-specific grey matter template. All native T_1 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 3 mm (full width half maximum = 8 mm).

VOXELWISE STATISTICAL ANALYSIS

In TBSS, a voxelwise 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 analyses contrasted baseline DTI data between controls and each FTD group separately. Longitudinal analyses contrasted DTI data acquired at the two time points (baseline and 12-month acquisition) within each group with a paired t -test. 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 FSL view (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.

RESULTS

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).

Patterns of Cross-sectional White and Grey Matter Changes in FTD Subtypes

Results from the DTI analyses showed the expected patterns of differential white matter changes at baseline in all

TABLE I. Demographic and clinical data of patients and control group

	bvFTD	PNFA	SD	Controls	<i>P</i>
Sex (M/F)	12(8/4)	10(6/4)	11(9/2)	15(8/7)	NS
Mean age (years)	63 ± 8	67 ± 11	62 ± 6	67 ± 6	NS
Education (yrs)	12 ± 3	12 ± 3	13 ± 3	14 ± 3	NS
ACE-R (max:100)	74 ± 12	79 ± 11	63 ± 12	94 ± 4	0.01 ^a
Disease duration (yrs)	4.8 ± 2.8	3.0 ± 0.58	5.4 ± 3.0	N/A	a
Scan interval (yrs)	0.9 ± 0.2	1.0 ± 0.0	1.0 ± 0.3	N/A	NS

Numerical values are illustrated in mean ± standard deviation.

Significant differences were observed in ACE-R between all FTD subtypes (bvFTD, PNFA and SD) and controls ($P < 0.01$).

^aSignificant differences between PNFA and SD.

Abbreviations: M, male; F, female; NS, not significant; ACE-R, Addenbrooke's Cognitive Examination-Revised; yrs, years; bvFTD, behavioral-variant frontotemporal dementia; PNFA, progressive non-fluent aphasia; SD, semantic dementia.

the FTD subtypes (Supporting Information Fig. S1; Acosta-Cabronero et al., 2011; Agosta et al., 2011; Mahoney et al., 2013; Schwindt et al., 2013). Differences in the data, however, were observed in the FTD subtypes depending on the DTI metrics.

Behavioral-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 (Supporting Information Fig. S1).

Progressive non-fluent 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 (Supporting Information Fig. S1).

Semantic dementia

Early white matter changes in SD were identified only in the left hemisphere (Supporting Information Fig. S1). 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.

Results from the VBM analyses showed the expected patterns of grey matter changes in all the FTD subtypes

(Supporting Information Fig. S2; Agosta et al., 2011; Boccardi et al., 2005; Mummery et al., 2000; Pan et al., 2012).

White matter abnormalities were found to extend beyond the locations of grey matter atrophy in two of the three FTD subtypes. This 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 parietal regions. In bvFTD, white matter changes extended from frontotemporal into the posterior temporal and occipital regions, compared to the predominant reduction in grey matter of the frontal and anterior temporal lobes bilaterally. In contrast, 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 (Supporting Information Fig. 2).

Patterns of Longitudinal White Matter Changes in FTD Subtypes

Behavioral-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 (Supporting Information Table S1) 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) (Fig. 1).

Progressive non-fluent aphasia

After 12 months, additional white matter abnormalities were observed in this group (anterior thalamic radiation, anterior cingulum, uncinate fasciculus, genu of corpus callosum, and the brainstem), with the changes becoming

Figure 1.

TBSS results of longitudinal white matter changes in bvFTD. Voxelwise 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. L = left; R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

more pronounced in the right compared to the left hemisphere (except for the anterior thalamic radiation which occurred on the left) (Fig. 2; Supporting Information Table SII). 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 ($P < 0.001$ uncorrected).

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) (Fig. 3). Longitudinal alterations in FA were

most extensive compared to the other metrics in SD, particularly in frontal white matter regions (Supporting Information Table SIII). Longitudinal changes in AxialD were found in the left temporal region only at the $P < 0.001$ uncorrected for multiple comparisons.

Finally, given the age-related changes affecting the white matter previously reported (Bartzokis et al., 2003; O'Sullivan et al., 2001; Salat et al., 2005), longitudinal analyses were also carried out in the control group in order to determine the ageing effect over 12 months. No significant changes in MD, AxialD and RadialD were observed between baseline and follow up scans. Small changes in FA were observed predominantly located in the frontal lobe white matter bilaterally (superior and inferior longitudinal fasciculi, inferior-fronto-occipital fasciculi and uncinate fasciculi). The magnitude of these changes, however,

Figure 2.

TBSS results of longitudinal white matter changes in PNFA. Voxelwise group changes from baseline are shown for FA, MD, and RadialD ($P < 0.05$, corrected for family wise error multiple comparisons). No significant change was found in AxialD. Results are overlaid on sagittal, axial, and coronal sections of the MNI standard brain. L = left; R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was about two to threefold less compared to the changes found in FTD groups over the same time period. These analyses confirmed that the white matter changes found in the FTD groups reflected disease, rather than ageing effects.

Overlaying White and Grey Matter Changes in FTD Subtypes After 12 Months

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 (Fig. 4). In bvFTD, the progression of grey matter atrophy was localized to the right frontotemporal 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 ($P < 0.001$ 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 (Fig. 4; Supporting Information Table SIV).

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.

Our investigations revealed that most white matter changes identified at follow up co-localized with the distribution of white matter abnormalities 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.

Figure 3.

TBSS results of longitudinal white matter changes in SD. Voxelwise 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. L = left; R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

This progression is particularly dramatic in bvFTD where the orbito-frontal 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. 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). 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. Of note, while none of the patients displayed clinical features of progressive supranuclear palsy at baseline or at the 12-month review, significant white matter change was observed in the brainstem over the 1-

year period in this group. In addition, the only PNFA case coming to autopsy showed pathological distribution consistent with progressive supranuclear palsy, highlighting the close relationship between these disorders (Josephs et al., 2005; Rohrer et al., 2010). Our findings suggest that the brainstem may be particularly vulnerable with disease progression in this group, even in the absence of clinical indicators, such as extra pyramidal or oculomotor disturbance. Finally, in SD, longitudinal white matter changes became widespread affecting white matter tracts bilaterally. Temporal regions continued to be affected, with additional frontal lobe involvement as disease progresses.

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 progressed only minimally over that time period with the damage remaining relatively focal. In contrast, white matter changes became widespread with bilateral alterations in frontotemporal regions and the damage

Figure 4.

Longitudinal changes in white matter and grey matter in FTD subtypes. Changes in FA (red) and grey matter density (yellow) over a 12-month period are illustrated for bvFTD, PNFA, and SD. All analyses were corrected for multiple comparisons at $P < 0.05$ 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. L = left; R = right. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

encroaching into the posterior white matter in all FTD subtypes.

Co-localization 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., 2010, 2011; Mahoney et al., 2013; Schwindt et al., 2013; 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., 2010, 2011; Mahoney et al., 2013; Schwindt et al., 2013; Zhang et al., 2013). Our study confirms the extensive pathological changes in white matter in FTD, changes that tend to extend beyond those observed grey matter atrophy, particularly with disease progression. 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, and MD), which measure different aspects of diffusion behavior 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 FA and RadialD 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 also likely explain the variable colocalization between white and grey matter changes reported above, given the single DTI measurement obtained in previous studies.

Animal studies have suggested that a decrease in AxialD correlates with axonal degeneration while an increase in RadialD suggests myelin loss (Song et al., 2003). Our findings indicate that 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 fibers 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., 2013; 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., 2012; 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, 2003).

Longitudinal imaging studies in FTD are much less common than cross-sectional investigations. Undoubtedly, longitudinal investigations present several challenges, not the least of which is to obtain good image quality in patients who are prone to head movements at two (or more) time points. In this study, another challenge was the limitations of TBSS in handling the registration process for longitudinal data, which may have increased the noise in the data. The undeniable advantage of longitudinal 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 change over time as the disease progresses. Arguably, our results need to be

taken with some caution. Whilst all cases underwent systematic clinical and cognitive assessments and met the most recent clinical diagnostic criteria for FTD, pathological confirmation was available for only two cases. Although our sample size may appear small, it is in keeping with similar work investigating brain changes in other neurodegenerative disorders (Acosta-Cabronero et al., 2011; Agosta et al., 2011; Mahoney et al., 2013; Schwindt et al., 2013).

CONCLUSION

This study investigated longitudinal white matter and grey matter changes concurrently in FTD. The results highlighted differential white matter changes at baseline and over a 12-month period in the three FTD subtypes. Our data show that the patterns of white matter changes are specific to each subgroup of FTD and longitudinal 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 alterations in diffusion 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 to establish the impact of therapeutic treatments in FTD syndromes over a relatively short time period.

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