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Cortical microstructure in the behavioural variant of frontotemporal dementia: looking beyond atrophy

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Cortical mean diffusivity has been proposed as a novel biomarker for the study of the cortical microstructure in Alzheimer's disease. In this multicentre study, we aimed to assess the cortical microstructural changes in the behavioural variant of frontotemporal dementia (bvFTD); and to correlate cortical mean diffusivity with clinical measures of disease severity and CSF biomarkers (neurofilament light and the soluble fraction beta of the amyloid precursor protein). We included 148 participants with a 3 T MRI and appropriate structural and diffusion weighted imaging sequences: 70 patients with bvFTD and 78 age-matched cognitively healthy controls. The modified frontotemporal lobar degeneration clinical dementia rating was obtained as a measure of disease severity. A subset of patients also underwent a lumbar puncture for CSF biomarker analysis. Two independent raters blind to the clinical data determined the presence of significant frontotemporal atrophy to dichotomize the participants into possible or probable bvFTD. Cortical thickness and cortical mean diffusivity were computed using a surface-based approach. We compared cortical thickness and cortical mean diffusivity between bvFTD (both using the whole sample and probable and possible bvFTD subgroups) and controls. Then we computed the Cohen's *d* effect size for both cortical thickness and cortical mean diffusivity. We also performed correlation analyses with the modified frontotemporal lobar degeneration clinical dementia rating score and CSF neuronal biomarkers. The cortical mean diffusivity maps, in the whole cohort and in the probable bvFTD subgroup, showed widespread areas with increased cortical mean diffusivity that partially overlapped with cortical thickness, but further expanded to other bvFTD-related regions. In the possible bvFTD subgroup, we found increased cortical mean diffusivity in frontotemporal regions, but only minimal loss of cortical thickness. The effect sizes of cortical mean diffusivity were notably higher than the effect sizes of cortical thickness in the areas that are typically involved in bvFTD. In the whole bvFTD group, both cortical mean diffusivity and cortical thickness correlated with measures of disease severity and CSF biomarkers. However, the areas of correlation with cortical mean diffusivity were more extensive. In the possible bvFTD subgroup, only cortical mean diffusivity correlated with the modified frontotemporal lobar degeneration clinical dementia rating. Our data suggest that cortical mean diffusivity could be a sensitive biomarker for the study of the neurodegeneration-related microstructural changes in bvFTD. Further longitudinal studies should determine the diagnostic and prognostic utility of this novel neuroimaging biomarker.

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Keywords: diffusion; magnetic resonance; frontotemporal dementia, biomarker

Abbreviations: bvFTD = behavioural variant of frontotemporal dementia; CATFI = catalan frontotemporal dementia initiative; FTLD = frontotemporal lobar degeneration; FTLD-CDR = frontotemporal lobar degeneration clinical dementia rating; FTLDNI = frontotemporal lobar degeneration neuroimaging initiative; NfL = neurofilament light; sAPPβ = soluble amyloid precursor protein beta fragment

Introduction

Frontotemporal lobar degeneration (FTLD) is a neuropathological construct encompassing multiple neurodegenerative diseases sharing partially overlapping patterns of frontal and/or temporal grey matter neurodegeneration (Bang *et al.*, 2015). The behavioural variant of frontotemporal dementia (bvFTD) is a common clinical presentation of FTLD (Seo *et al.*, 2018). Clinically, bvFTD is characterized by progressive personality changes followed by social, cognitive and functional deterioration (Ranasinghe *et al.*, 2016). With the exception of genetically determined cases, the diagnosis of bvFTD relies on the clinical and neuroimaging features (Rascovsky *et al.*, 2011; Wood *et al.*, 2013). The refinement of the diagnostic criteria proposed by the frontotemporal dementia consortium has been an important step forward to improve the diagnosis of the bvFTD. Furthermore, these criteria have shown a good diagnostic value in pathology-confirmed cases (Rascovsky *et al.*, 2011; Chare *et al.*, 2014; Balasa *et al.*, 2015; Perry *et al.*, 2017; Seo *et al.*, 2018). In the frontotemporal dementia consortium criteria, the presence of frontal and/or temporal atrophy increases the diagnostic certainty once the clinical criteria for possible bvFTD are met. However, a number of patients are still misdiagnosed with other neurodegenerative and non-neurodegenerative diseases (Bang *et al.*, 2015). Several factors, such as the absence of prominent cortical atrophy in up to a third of the patients (Rascovsky *et al.*, 2011; Ranasinghe *et al.*, 2016), may contribute to misdiagnosis. Conversely, possible bvFTD may include both neurodegenerative cases in early phases of the disease and non-neurodegenerative phenocopies (Khan *et al.*, 2012; Gossink *et al.*, 2016). Thus, the development of novel biomarkers able to increase the diagnostic certainty of FTLD is essential (Lam *et al.*, 2013; Downey *et al.*, 2015; Binney *et al.*, 2017; Meeter *et al.*, 2017). These are key aspects for the detection of patients with FTLD-related syndromes, especially at the earliest phase in clinical practice and for the selection of candidates to trials with protein-specific targeted therapies that may be more effective in earlier stages (Elahi and Miller, 2017).

Most neuroimaging studies in bvFTD have been focused on the cortical macrostructure with different metrics (grey matter density in voxel-based morphometry studies or cortical thickness in surface-based analyses) (Mahoney *et al.*, 2014*a*, *b*; Elahi *et al.*, 2017; Meeter *et al.*, 2017) or white matter microstructural properties (namely diffusion tensor imaging metrics such as, fractional anisotropy). However, diffusion tensor imaging can also be used to measure the magnitude of diffusivity (mean diffusivity), in the cerebral cortex (Weston *et al.*, 2015; Montal *et al.*, 2017). Higher cortical mean diffusivity values reflect microstructural disorganization and disruption of cellular membranes, and have been proposed as a sensitive biomarker that might antedate macroscopic cortical changes (Weston *et al.*, 2015). However, only a single small study has assessed mean diffusivity changes in frontotemporal dementia (Whitwell *et al.*, 2010). In that previous study, no clear differences were found between grey matter density and grey matter mean diffusivity, as assessed on a voxel-based approach. However, the voxel-based approach may fail to capture the subtle tissue-specific changes that take place at the cortical level (Weston *et al.*, 2015).

In bvFTD, there are no validated pathophysiological biomarkers to reflect the underlying pathology, with the exception of pathogenic mutations that predict specific FTLD subtypes. However, CSF biomarkers may also contribute to

our understanding of FTLD pathophysiology (Meeter *et al.*, 2017; Lleo *et al.*, 2018). Particularly, the CSF levels of neurofilament light (NfL) (an axonal cytoskeletal constituent essential for axonal growth) have shown to be a useful neurodegeneration biomarker in FTLD-related syndromes (Scherling *et al.*, 2014; Menke *et al.*, 2015). In addition to NfL, we have recently shown that the levels of the soluble amyloid precursor protein beta fragment (sAPPβ) (Alcolea *et al.*, 2017) may be useful to track neurodegeneration in frontotemporal structures in frontotemporal dementia (Alcolea *et al.*, 2017; Illán-Gala I *et al.*, 2018).

In this multicentre study, we aimed to assess the cortical mean diffusivity changes in a large multicentre cohort of patients with bvFTD, and to correlate these changes with clinical measures of disease severity (FTLD-CDR) and CSF biomarkers (NfL and sAPPβ). We hypothesized that cortical mean diffusivity may be more sensitive than cortical thickness to detect the cortical changes associated with bvFTD.

Materials and methods

Study participants

Participants were recruited in three different centres from two collaborative studies: The Catalan Frontotemporal Dementia Initiative (CATFI) and the Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI).

The CATFI is a multicentre study focused on the development of novel biomarkers and therapeutic interventions for patients suffering from frontotemporal dementia. The CATFI study includes patients from three centres [Hospital de Sant Pau (HSP), Hospital Clínic de Barcelona (HCB) and Hospital Arnau de Vilanova]. The principal investigator of the CATFI study is Dr Alberto Lleó. The primary goals of FTLDNI are to identify neuroimaging modalities and methods of analysis for tracking FTLD and to assess the value of imaging versus other biomarkers in diagnostic roles. The principal investigator of FTLDNI is Dr Howard Rosen at the University of California, San Francisco (UCSF). For up-to-date information on participation and protocol, please visit: http://memory.ucsf.edu/research/studies/nifd.

The inclusion criteria in this study were: (i) diagnosis of possible or probable bvFTD according to the frontotemporal dementia consortium criteria (Rascovsky *et al.*, 2011); and (ii) 3 T MRI study available for structural and cortical mean diffusivity analysis (see below for details). In both cohorts the diagnosis was made by neurologists with expertise in the evaluation the FTLD-related syndromes after an extensive neurological and neuropsychological evaluation. Moreover, patients were followed longitudinally at each centre to ascertain if they presented a progressive clinical deterioration or developed a second FTLD-related syndrome (i.e. amyotrophic lateral sclerosis or a progressive supranuclear palsy phenotype). Because the diagnosis of bvFTD has been related to non-neurodegenerative conditions in some cases that do not show the typical clinical progression, we identified patients with bvFTD with increased certainty of underlying FTLD when any of the following criteria were met: (i) clinical evidence of disease progression (clinical deterioration evidenced during follow-up or progression to a second phenotype related to FTLD); (ii) genetic confirmation of FTLD (identification of a pathogenic mutation); and (iii) confirmation of FTLD in those patients with neuropathological evaluation.

Figure 1 shows the flowchart of the sample composition. A total of 192 participants with appropriate 3 T structural and diffusion-weighted MRI were considered for analysis. Of these, 44 (23%) participants were excluded due to quality control issues or processing errors. All the excluded cases were patients with bvFTD.

Clinical measures of disease severity

The modified FTLD-CDR was obtained as described previously, as a measure of bvFTD disease severity (Knopman *et al.*, 2008). Higher scores in the FTLD-CDR reflect a greater disease severity.

Genetic studies

Patients were screened for genetic mutations known to cause autosomal dominant inheritance of frontotemporal dementia as previously reported (Perry *et al.*, 2017; Illán-Gala I *et al.*, 2018).

Pathological assessment

Neuropathological assessments were performed at the Barcelona Brain bank ($n = 1$) or at UCSF ($n = 5$) following previously described procedures (Tartaglia *et al.*, 2010; Balasa *et al.*, 2015). Pathology-proven FTLD cases were classified in one of the major molecular subtypes (tau, TDP-43, FUS or unclassifiable).

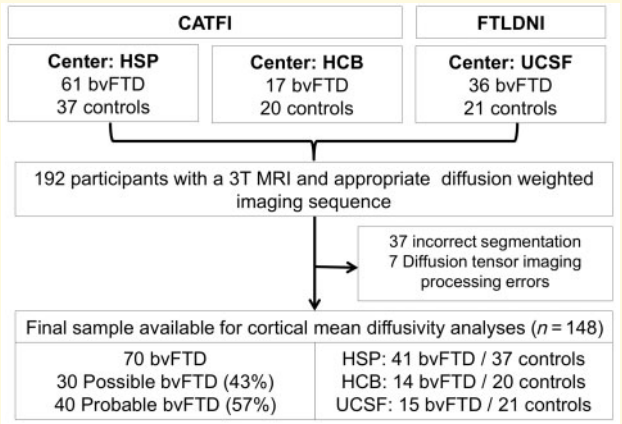

Figure 1 Flowchart of the sample composition.
HSP = Hospital de Sant Pau; HCB = Hospital Clínic de Barcelona; UCSF = University of California San Francisco.

MRI acquisition

MRIs (3 T) were acquired at three different sites. The acquisition parameters by centre can be found in the Supplementary material. All centres had a structural MPRAGE T_1-weighted acquisition of approximately $1 \times 1 \times 1$ mm isotropic resolution and an EPI diffusion-weighted acquisition of at least $2.7 \times 2.7 \times 2.7$ mm isotropic resolution.

Possible/probable classification according to MRI atrophy on visual inspection

To determine the presence of significant frontotemporal atrophy consistent with the diagnosis of probable bvFTD according to the frontotemporal dementia consortium criteria (Rascovsky *et al.*, 2011), all the MRIs from bvFTD participants analysed in this study ($n = 114$) were visually inspected by two independent raters blinded to the clinical data in order to determine the presence of significant frontotemporal atrophy to dichotomize the participants into possible bvFTD (patients with bvFTD with a negative or conflicting atrophy rating) or probable bvFTD (patients with bvFTD rated as positive atrophy by the two raters) (Rascovsky *et al.*, 2011).

CSF sampling and analysis

A subset of 32 CATFI patients also had CSF available. We measured the CSF levels of NfL and sAPPβ as described previously (Alcolea *et al.*, 2014, 2015, 2017). All biomarkers were analysed at the Sant Pau Memory Unit Laboratory with commercially available ELISA kits (NF-light, Uman Diagnostics; human sAPPβ-w, highly sensitive, IBL).

Cortical thickness processing

Cortical thickness reconstruction was performed with the Freesurfer package v5.1 (http://surfer.nmr.mhg.hardvard.edu) using a procedure that has been described in detail elsewhere (Fischl and Dale, 2000). All individual cortical reconstructions were visually inspected in a slice-by-slice basis to check for accuracy of the grey/white matter boundary segmentation. From the initial 114 bvFTD subjects with 3 T MRI available from the three centres, 37 (32.5%) were excluded because of segmentation issues. Cognitively healthy control scans did not require manual editing. Finally, each individual reconstructed brain was registered, and cortical thickness maps were morphed, to the *fsaverage* standard surface provided by Freesurfer, using a spherical registration, enabling an accurate inter-subject matching of cortical locations for the computation of further statistics. Prior to statistical analyses, we smoothed the cortical thickness maps using a Gaussian kernel with full-width at half-maximum of 10 mm as implemented in Freesurfer (Hagler *et al.*, 2006).

Cortical mean diffusivity processing

We used a previously described homemade surface-based approach to process cortical diffusion MRI (Montal *et al.*, 2017). Recent studies have shown the potential of surface-based methods to measure microstructural changes in neurodegenerative diseases (Montal *et al.*, 2017; Parker *et al.*, 2018) and the cortical architecture (Ganepola *et al.*, 2018). An important advantage of these methods is the mitigation of partial volume effects or kernel-sensitive CSF signal inclusion during the smoothing step (Coalson *et al.*, 2018). Briefly, diffusion weighted imaging data were first corrected for motion effects applying a rigid body transformation between the b = 0 image and the diffusion-weighted acquisitions. Then, after removing non-brain tissue using the Brain Extraction Tool, diffusion tensors were fitted and mean diffusivity was computed using the FSL's dtifit command. We then computed the affine transformation between the skull-stripped b0 and the segmented T_1-weighted volume using a boundary-based algorithm as implemented in Freesurfer's bbregister. This approach takes advantage of the accurate segmentation of the white matter surface and pial surface obtained during the Freesurfer's segmentation (cortical thickness processing section), to accurately register the b0 and the T_1-weighted image, maximizing the intensity gradient across grey matter and white matter between both volumes. At this point, all the diffusion to T_1 registrations were visually inspected to exclude those subjects with an erroneous co-registration. Then, the mean diffusivity volume for each individual was sampled at the midpoint of the cortical ribbon (half the distance along the normal vector between the white matter surface and the grey matter surface) and projected to each individual surface reconstruction obtained during the Freesurfer processing, to create a surface map of cortical mean diffusivity (using Freesurfer's mri_vol2surf command). Finally, individual cortical mean diffusivity maps were normalized to an average standard surface using a spherical registration, enabling an accurate inter-subject matching of cortical locations for the statistical analyses. Prior to statistical analyses, we applied a Gaussian kernel of 15 mm as implemented in Freesurfer to obtain equivalent data effective smoothing between cortical thickness and cortical mean diffusivity (La Joie *et al.*, 2012; Bejanin *et al.*, 2018).

Cortical mean diffusivity harmonization between centres

Diffusion tensor imaging metrics are sensitive to acquisition parameters (Zhu et *al.*, 2011). Thus, harmonization approaches are required to mitigate centre-specific differences in multicentre studies. We applied a multi-centre harmonization algorithm based on ComBat to reduce centre-specific differences in cortical mean diffusivity quantifications prior to any statistical analysis (Fortin *et al.*, 2017). Briefly, ComBat uses an empirical Bayes framework to estimate the additive (mean) and multiplicative (variance) contribution of each site, at each vertex, for a specific diffusion tensor imaging metric, and corrects these effects. Importantly, this approach allows the inclusion of biological information (such as clinical group, age or biomarkers), and it has been reported to preserve within-site biological variability, thereby increasing the statistical power.

Statistical methods

Group differences in the clinical and biomarker data were assessed using *t*-test or ANOVA for continuous variables, and chi-squared tests were used for dichotomous or categorical data. Biomarker values not following a normal distribution were log-transformed. Statistical analyses were performed with the IBM SPSS Statistics 25 (IBM corp.) software. Statistical significance for all tests was set at 5% ($\alpha = 0.05$), and all statistical tests were two-sided.

We first performed group comparisons for cortical mean diffusivity and cortical thickness with a two-class general linear model, as implemented in Freesurfer, comparing bvFTD and the cognitively healthy controls groups. These analyses were repeated for each centre independently. Moreover, as it has been reported that some possible bvFTD cases may represent either non-neurodegenerative cases or cases with a slowly progressive clinical course, we also compared the patterns of cortical thickness and cortical mean diffusivity in both the probable and possible subgroups. We then performed a vertexwise partial correlation analysis in the bvFTD group between the cortical mean diffusivity and cortical thickness and the log-transformed CSF sAPPβ and NfL values, in addition to the FTLD-CDR. Specifically, a general linear model was created in which cortical mean diffusivity or cortical thickness was included as the dependent variable, and CSF values and FTLD-CDR scores were independent variables. We included age, sex, and centre as nuisance variables in the cortical thickness analysis. In mean diffusivity analysis, only age and sex were included since diffusion tensor imaging data were already harmonized between centres in a previous step. The correlation between both metrics and FTLD-CDR was also assessed segregating the bvFTD group into possible and probable. Only results that survived multiple comparisons (family wise error < 0.05) based on Monte Carlo simulation with 10 000 repeats as implemented in Freesurfer are presented. We used a stringent threshold of $\alpha = 0.001$ for the group analyses and a threshold of $\alpha = 0.05$ for the correlation analyses. A full description of the multiple comparisons methodology can be found in the Supplementary material.

We computed the Cohen's *d* effect size metric for both cortical thickness and cortical mean diffusivity, in a vertex-wise basis, to obtain a topographical representation of the effect size for the group comparison between patients with bvFTD and cognitively healthy controls. Effect size computation was restricted to cortical regions showing statistically significant differences between bvFTD and cognitively healthy controls for either cortical thickness or cortical mean diffusivity. We then computed the difference between the cortical thickness and cortical mean diffusivity effect size maps to obtain a topographical representation of the net effect size for each metric. For the figure projection and design, we used a freely available python library to overlay the results into the standard fsaverage surface (Pysurf: https://pysurfer.github.io).

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Results

Demographics and sample composition

Table 1 shows the demographics, clinical and neuroimaging features of the participants in the study. Age at MRI and years of education was similar between the bvFTD and healthy control groups. There were more females in the cognitively healthy control group than in the bvFTD group [$\chi^2(1) = 23.090$; $P < 0.001$]. Age at symptom onset, age at MRI, time from symptom onset to MRI, sex distribution, education, FTLD-CDR, and follow-up time were similar between the possible and probable bvFTD groups. However, the proportion of patients with an increased certainty of FTLD at the end of follow-up was higher in the probable bvFTD group than in the possible bvFTD group [$\chi^2(1) = 8.089$; $P = 0.004$]. As shown in Fig. 1, 44 of 114 (38.6%) bvFTD participants were excluded because of segmentation or diffusion weighted imaging processing errors. The excluded patients had higher FTLD-CDR than the included bvFTD participants [$t(92) = 2.041$; $P = 0.044$; Supplementary Table 3].

Group comparison of cortical thickness and cortical mean diffusivity

First, we compared cortical thickness and cortical mean diffusivity between bvFTD and cognitively healthy controls. As shown in Fig. 2, the bvFTD group showed cortical thinning in the prefrontal cortex, the insula, the cingulate gyrus (anterior, dorsal and posterior), the orbitofrontal cortex, the anterior temporal pole, the lateral and medial temporal lobe, the angular gyrus and the precuneus. The cortical mean diffusivity map involved more regions, encompassing the whole of the frontal and temporal cortices, and extending to posterior regions such as the inferior parietal and occipital lobe. Thus, while cortical thickness and cortical mean diffusivity maps showed a partial overlap, cortical mean diffusivity changes extended beyond the areas of cortical thinning. Of note, we observed similar patterns of cortical thickness and cortical mean diffusivity changes when each cohort was analysed separately (data not shown).

We found moderate-to-high effect sizes for cortical thickness in the prefrontal cortex, the insula, the anterior and posterior cingulate gyrus, the lateral and medial temporal lobe and the precuneus bilaterally (Fig. 2, bottom). For cortical mean diffusivity, we obtained widespread maps of moderate-to-high effect sizes. The highest effect sizes for cortical mean diffusivity were observed at the frontal and temporal cortex bilaterally. Importantly, the effect sizes of cortical mean diffusivity were higher than the effect sizes of

Table 1 Demographics, clinical and neuroimaging features of the participants

Characteristics	Possible bvFTD	Probable bvFTD	All bvFTD	Cognitively healthy controls
n (% of bvFTD)	30 (43)	40 (57)	70 (100)	78
Age at symptom onset, years	60.2 ± 11.4[a]	57.9 ± 8.8[a]	58.8 ± 10	-
Age at MRI, years	65.8 ± 10.9[a]	62.4 ± 9.2[a]	63.8 ± 10[a]	62.3 ± 6.1[a]
Time from onset to MRI, years	5.5 ± 4.2[a]	4.5 ± 3.1[a]	4.9 ± 3.6	-
Sex male/female, *n*	24/6[b]	27/13[b]	51/19[b]	26/52[c]
Education, years	12.5 ± 5.6[a]	13 ± 5.4[a]	12.7 ± 5.5[a]	13.4 ± 4.3[a]
FTLD-CDR[f]	6.4 ± 3.7[a]	8.3 ± 4[a]	7.5 ± 4	-
Follow-up time, years	1.7 ± 1.4[a]	1.9 ± 2[a]	1.8 ± 1.7	-
Last reported phenotype	24 bvFTD 1 bvFTD with progressive aphasia 2 FTD-ALS 3 PSP-CBD	27 bvFTD 4 bvFTD with progressive aphasia 7 FTD-ALS 2 PSP-CBD	51 bvFTD 5 bvFTD with progressive aphasia 9 FTD-ALS 5 PSP-CBD	
Increased certainty of underlying FTLD (% of cases)	21 (70)[d]	38 (95)[e]	59 (84.3)	-
Definitive bvFTD (% of cases)	7 (23.3)[a] 4 *C9orf72* 0 *GRN* 1 *MAPT* 0 *TARDBP* 2 FTLD-TDP (1 *C9orf72*) 1 FTLD-Tau	12 (30)[a] 7 *C9orf72* 2 *GRN* 0 *MAPT* 1 *TARDBP* 1 FTLD-TDP (1 *TARDBP*) 2 FTLD-Tau	19 (27.1) 11 *C9orf72* 2 *GRN* 1 *MAPT* 1 *TARDBP* 3 FTLD-TDP (1 *C9orf72* and 1 *TARDBP*) 3 FTLD-Tau	-

Demographics, clinical and neuroimaging features of the participants. Values reported are mean ± standard deviation.
[a]Non-significant differences.
[b]Different from the healthy control group ($P < 0.05$).
[c]Different from the all bvFTD group ($P < 0.05$).
[d]Different from the probable bvFTD group ($P < 0.05$).
[e]Different from the possible bvFTD group ($P < 0.05$).
[f]Available in 59 of the 70 (84.3%) bvFTD patients.
FTD-ALS = frontotemporal dementia-amyotrophic lateral sclerosis; FTLD-Tau = tau subtype of frontotemporal lobar degeneration; FTLD-TDP = transactive response DNA-binding protein 43 kDa subtype of frontotemporal lobar degeneration; PSP-CBD = progressive supranuclear palsy-corticobasal degeneration.

cortical thickness in bvFTD-related areas such as the anterior and dorsal cingulate, the prefrontal dorsal cortex and the insula in both hemispheres. In these areas we observed moderate-to-high net effect sizes favouring cortical mean diffusivity.

Cortical thickness and cortical mean diffusivity in possible and probable bvFTD

We then assessed cortical thickness and cortical mean diffusivity separately in the possible and probable bvFTD subgroups (Fig. 3). In the probable bvFTD group we observed extensive clusters of cortical thinning that included essentially the same regions typically involved in the bvFTD that were observed in the Fig. 2. Similar to what we observed in the primary analyses, the cortical mean diffusivity changes were more widespread than the cortical thickness changes as shown in the overlap map of Fig. 3 (top). We also observed moderate-to-high net effect sizes favouring cortical mean diffusivity in the rostral middle frontal, superior frontal, anterior cingulate, the insula and in more posterior regions (posterior temporal, precuneus and occipital lobe) (Fig. 3, top). In the possible bvFTD subgroup, we observed small clusters of cortical thinning in the insula, and the medial temporal lobe in both hemispheres. Interestingly, we observed extensive cortical mean diffusivity increases in the dorsal and medial prefrontal cortex, as well as in the supplementary motor cortex and the frontal pole in both hemispheres (Fig. 3, bottom). In the possible bvFTD group, we also observed moderate-to-high net effect sizes favouring cortical mean diffusivity in the rostral middle frontal and superior frontal cortex in both hemispheres (Fig. 3, bottom).

Relationship between cortical thickness and cortical mean diffusivity with the FTLD-CDR

We next evaluated the capacity of cortical thickness and cortical mean diffusivity to reflect the disease severity in the bvFTD as measured by the FTLD-CDR scale. When pooling together all the bvFTD subjects, we observed an

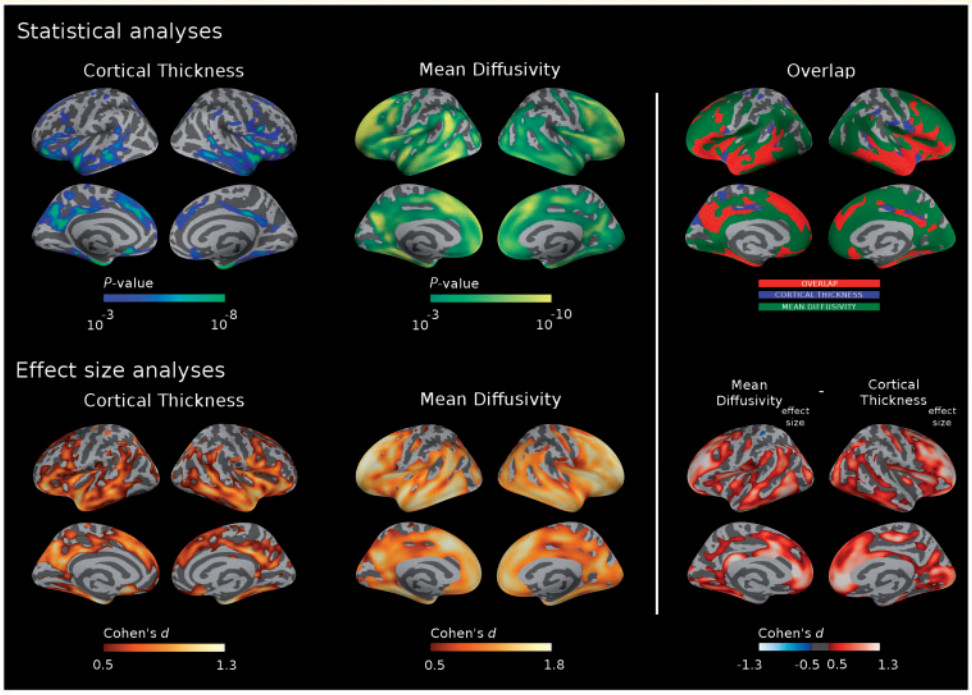

Figure 2 Group comparison of cortical thickness and cortical mean diffusivity between bvFTD and cognitively healthy controls. *Top*: Statistically significant results between all bvFTD and cognitively healthy controls for cortical thickness and cortical mean diffusivity. Regions in blue represent thinner cortex in the bvFTD group, whereas regions in green represent higher cortical mean diffusivity in the bvFTD group. For illustration purposes, we included the overlapping map between both metrics (*top right*). Cortical thickness analyses were adjusted for age, sex and centre. Mean diffusivity analyses were adjusted for age and sex after a harmonization step. Only the clusters that survived family-wise error correction $P < 0.05$ are shown. *Bottom*: Medium to large effect sizes between the bvFTD and cognitively healthy controls for both cortical thickness and cortical mean diffusivity. The orange-gold colour represents higher effect size. In addition, the difference between both maps of effect size is displayed (*bottom right*). The red-white colour represents grey matter areas where the cortical mean diffusivity has higher effect size than cortical thickness.

inverse correlation between FTLD-CDR scores and cortical thickness in small clusters in the inferior frontal gyrus, the anterior insula, the anterior temporal pole and the medial temporal lobe in both hemispheres and a correlation in the medial orbitofrontal cortex and in the precuneus in the left hemisphere. We observed larger clusters of significant positive correlations between cortical mean diffusivity and FTLD-CDR scores in both hemispheres (Fig. 4, top). Similar results were found when restricting the analyses to the probable bvFTD group (Fig. 4, middle). When restricting the analysis to the possible bvFTD, we did not find any correlation between cortical thickness and FTLD-CDR scores. However, cortical mean diffusivity was positively associated with FTLD-CDR scores in the anterior cingulate, frontal insula and lateral temporal in both hemispheres (Fig. 4, bottom).

Correlation of cortical thickness and mean diffusivity changes with CSF biomarkers

Finally, we assessed the correlation of cortical thickness and cortical mean diffusivity with CSF NfL and sAPPβ levels. CSF NfL levels were negatively correlated with cortical thickness in dorsolateral and medial prefrontal areas of the frontal lobe. The correlation between CSF NfL levels and cortical mean diffusivity included those areas, but also areas in the temporal and parietal lobes (Fig. 5, top). CSF sAPPβ levels were positively correlated with cortical thickness in regions of the prefrontal cortex, the insula, the temporo-parietal union and the lateral temporal cortex. The negative correlation between CSF sAPPβ levels and cortical mean diffusivity extended to more widespread frontal and temporal regions, as well as to posterior regions (Fig. 5, bottom).

Discussion

In this study we investigated the value of cortical mean diffusivity as a biomarker in bvFTD in a large multicentre sample. We showed that altered cortical mean diffusivity not only coincided with areas that showed cortical thinning, but also involved other areas that typically become affected with disease progression (Binney *et al.*, 2017). Furthermore, we found cortical mean diffusivity was

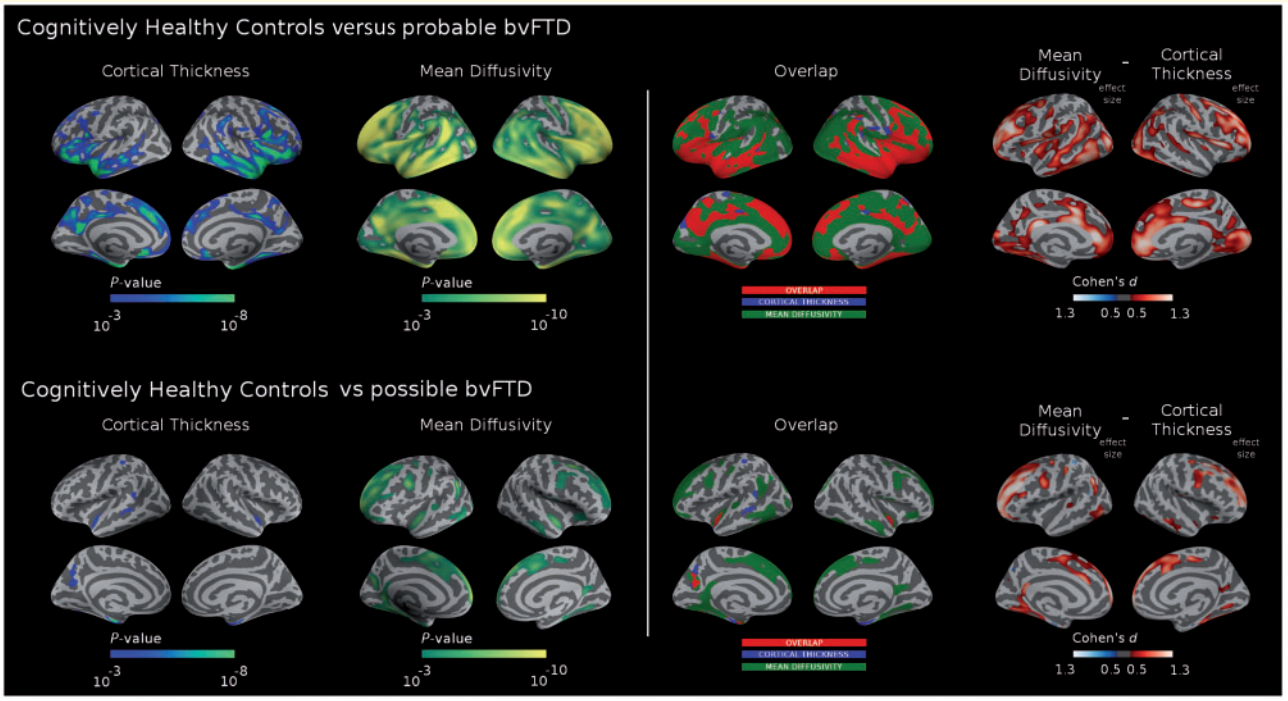

Figure 3 Group comparison of cortical thickness and cortical mean diffusivity between patients with possible and probable bvFTD and cognitively healthy controls. Cortical thickness and cortical mean diffusivity group comparisons between probable (*top*) and possible (*bottom*) bvFTD against cognitively healthy controls. We included the overlapping map (*top* and *bottom*) between both metrics. Cortical thickness analyses are adjusted by age, sex and centre. Mean diffusivity analyses were adjusted by age and sex after a harmonization step. Only clusters that survived family-wise error correction ($P < 0.05$) are shown. For visualization purposes, different colour codes were used for cortical thickness and cortical mean diffusivity. In addition, the net difference in effect size is displayed for probable bvFTD (*top right*) and possible bvFTD (*bottom right*). The red-white colour represents grey matter areas where the cortical mean diffusivity has higher effect size than cortical thickness.

increased in patients classified as possible bvFTD that had only minimal cortical thinning. Clinical measures of disease severity (FTLD-CDR) and CSF neuronal biomarkers (CSF NfL and sAPPβ levels) showed a more widespread correlation with cortical mean diffusivity than with cortical thickness. Taken together, these findings suggest that cortical mean diffusivity might be more sensitive than cortical thickness to detect the earliest disease-related cortical changes in bvFTD.

Cortical mean diffusivity has been recently proposed as a sensitive biomarker for the detection of the earliest cortical changes in sporadic Alzheimer's disease (Weston *et al.*, 2015; Montal *et al.*, 2017). We show, for the first time in bvFTD using a surface-based approach, that cortical mean diffusivity increases spread beyond the areas of cortical thinning in bvFTD, even in patients with possible bvFTD. Most previous studies using diffusion tensor imaging in patients with bvFTD have focused on the white matter, probably because of the technical difficulties in the study of cortical microstructure (Agosta *et al.*, 2015; Papma *et al.*, 2017). We identified a single previous small study (with 16 patients with bvFTD) assessing cortical diffusion tensor imaging in the bvFTD using a volume-based approach (Whitwell *et al.*, 2010). This study found overlapping patterns between atrophy and increases on cortical mean diffusivity. Our study builds on these results using a larger sample, a surface-based approach, and the inclusion of patients with bvFTD at milder disease stages. Consequently, we were able to show the added value of cortical mean diffusivity as a more sensitive biomarker in bvFTD over cortical thickness.

We found minimal cortical thinning when comparing possible patients with bvFTD and controls. However, we observed extensive cortical mean diffusivity increases in regions known to be affected in bvFTD (Brettschneider *et al.*, 2014; Schroeter *et al.*, 2014; Irwin *et al.*, 2016). Moreover, we calculated effect size maps to quantify the impact of cortical thickness and cortical mean diffusivity for the differentiation of patients with bvFTD from controls. Importantly, we obtained moderate-to-high net effect size favouring cortical mean diffusivity in critical bvFTD-related cortical regions such as the anterior cingulate, the prefrontal dorsal cortex and the insula. The suggestion that cortical mean diffusivity may be more sensitive than cortical thickness to detect the bvFTD cortical changes is further supported by our correlation analyses with the FTLD-CDR and CSF NfL and sAPPβ levels. Both the clinical measures of disease severity and the CSF biomarkers showed a better correlation with cortical mean diffusivity than with cortical thickness. The FTLD-CDR has been

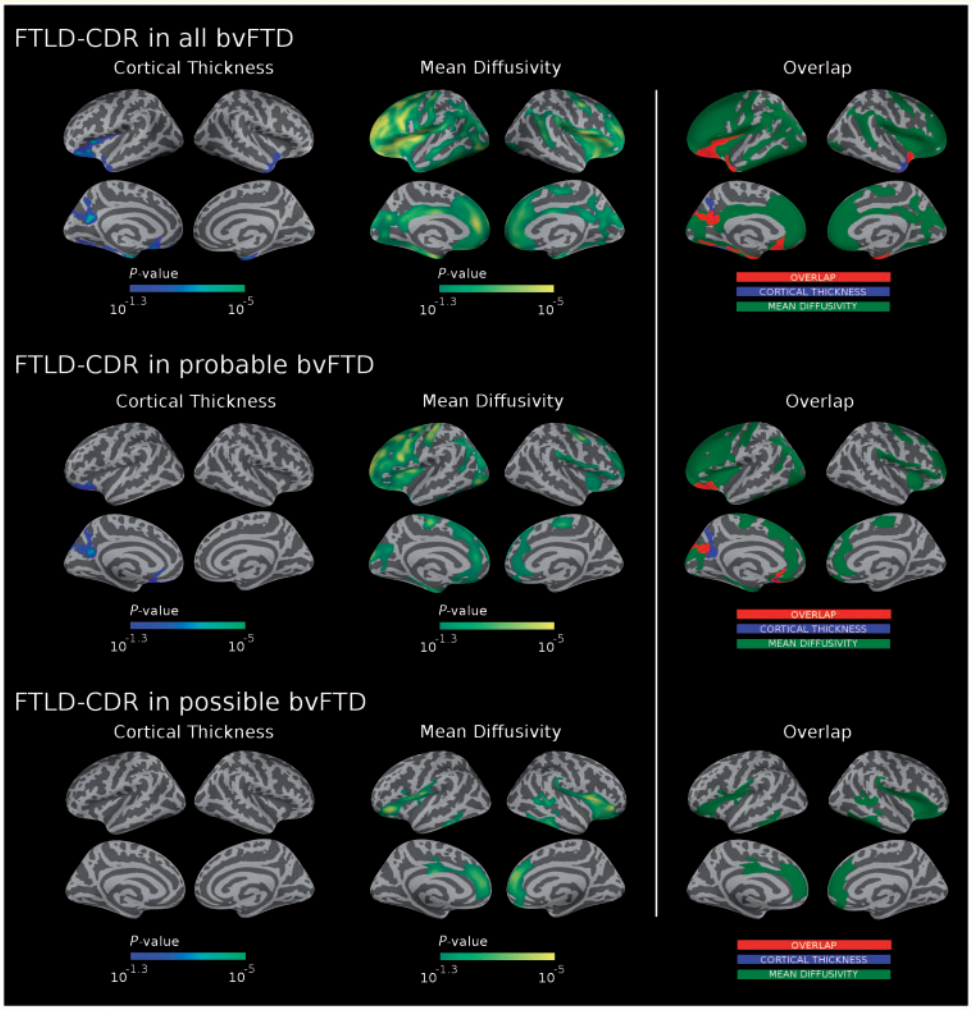

Figure 4 Relationship between cortical thickness and cortical mean diffusivity with the FTLD-CDR score. Correlation of cortical mean diffusivity with the frontotemporal lobar degeneration clinical dementia rating score in the whole sample (*top*), probable bvFTD subgroup (*middle*) and possible bvFTD subgroup (*bottom*). Small regions of cortical thinning associated with higher FTLD-CDR scores (blue) were found in the probable subgroup, whereas extensive areas of increases of cortical mean diffusivity related to increases in FTLD-CDR scores (green) were found in both subgroups. Cortical thickness analyses were adjusted for age, sex and centre. Mean diffusivity analyses were adjusted for age and sex after a harmonization step. The overlap between both maps is displayed on the right (*top* and *bottom*).

validated as a tool for disease monitoring in clinical trials (Knopman *et al.*, 2008). Although the FTLD-CDR scores also correlated with cortical thickness in some small frontotemporal clusters, we found a substantially widespread correlation with cortical mean diffusivity. Moreover, when restricting the analyses in the possible bvFTD subgroup, only associations between cortical mean diffusivity and FTLD-CDR scores were found. This finding supports a possible role for cortical mean diffusivity as a candidate neuroimaging biomarker for disease staging.

To evaluate the role of cortical mean diffusivity as a neurodegeneration biomarker further, we investigated its correlation with CSF biomarkers in a subgroup of patients. NfL is one of the major constituents of the axonal cytoskeleton and plays an important role in axonal transport. The measurement of NfL levels both in the CSF and in serum correlates with disease severity, progression and survival in multiple neurodegenerative diseases (Landqvist Waldö *et al.*, 2013; Scherling *et al.*, 2014; Pijnenburg *et al.*, 2015; Meeter *et al.*, 2016; Rohrer *et al.*, 2016; Wilke *et al.*, 2016). We also measured CSF sAPPβ levels, as we have previously shown that this biomarker correlates with frontotemporal neurodegeneration in FTLD-related syndromes (Alcolea *et al.*, 2017; Illán-Gala *et al.*, 2018). The association between cortical mean diffusivity and CSF values further reinforces the notion that cortical mean diffusivity changes reflect the underlying neurodegeneration.

Although we acknowledge that it is possible that some patients classified as possible bvFTD may not have underlying FTLD (Devenney *et al.*, 2016; Gossink *et al.*, 2016), recent studies in deep-phenotyped cohorts have shown that a significant proportion of bvFTD cases do not have

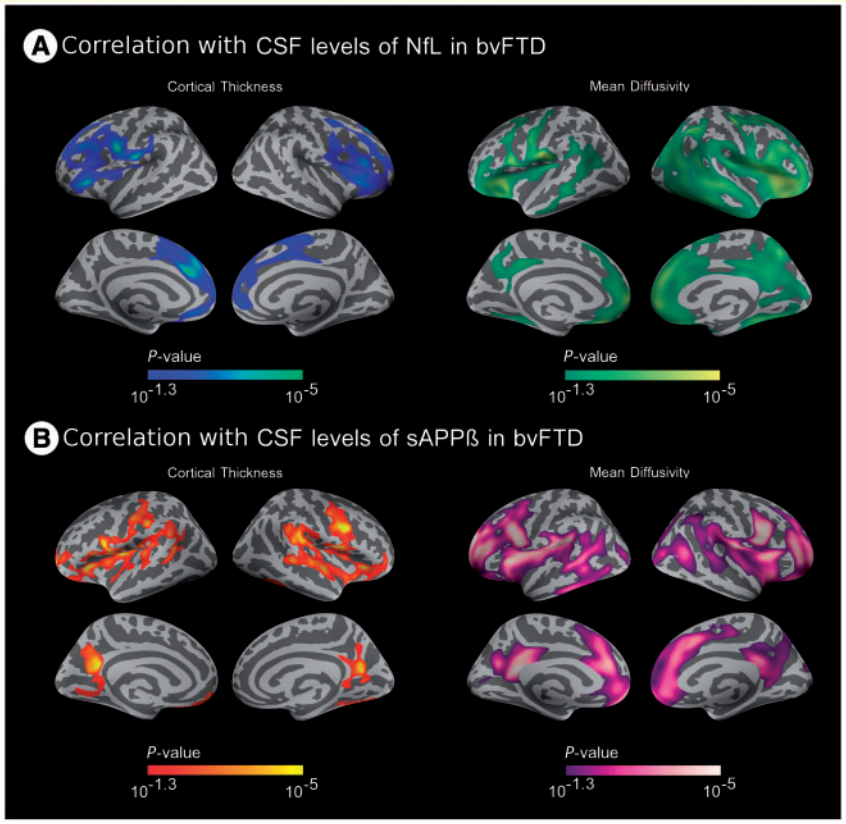

Figure 5 Correlation of cortical thickness and cortical mean diffusivity with CSF biomarkers. Relationship of cortical thickness and cortical mean diffusivity with the CSF levels of NfL (*top*) and the CSF levels of sAPPβ (*bottom*) in the subgroup of bvFTD participants with CSF sample available for analysis ($n = 32$). As NfL and sAPPβ values were not normally distributed, we used log-transformed values for these biomarkers. NfL levels negatively correlated with cortical thickness (blue) and positively correlated with cortical mean diffusivity (green). sAPPβ positively correlated with cortical thickness (red) and negative correlated with cortical mean diffusivity (purple). Cortical thickness analyses were adjusted for age, sex and centre. Mean diffusivity analyses were adjusted for age and sex after a harmonization step. Only clusters that survived familywise error correction at $P < 0.05$ are shown.

frontotemporal atrophy and may be characterized by a slower disease course (Rascovsky *et al.*, 2011; Ranasinghe *et al.*, 2016). In the present study, 70% of patients classified as possible bvFTD were found to have an increased certainty of underlying FTLD as suggested by follow-up, genetic and neuropathological information available. Indeed, longitudinal decline was observed in most possible patients with bvFTD and psychiatric diagnoses were excluded by expert clinicians. Of note, four cases classified as possible bvFTD were found to have a *C9orf72* expansion, a finding that has been previously reported in different cohorts (Khan *et al.*, 2012; Gómez-Tortosa *et al.*, 2014; Devenney *et al.*, 2018; Llamas-Velasco *et al.*, 2018). Thus, we propose that the patients classified as possible bvFTD are at high risk of having underlying FTLD and that our cortical mean diffusivity results support that at least a proportion of possible patients with bvFTD have a neurodegenerative disease. Cortical mean diffusivity may be a relevant tool for increasing the diagnostic certainty in these 'slowly progressive' bvFTD patients without overt frontotemporal atrophy (Davies *et al.*, 2006; Khan *et al.*, 2012).

Taken together, our findings support the role of cortical mean diffusivity as a novel potential neurodegeneration biomarker in bvFTD. We hypothesize that cortical mean diffusivity may be a sensitive tool for the refinement and monitoring of the very earliest cortical changes genetically determined FTLD (Rohrer *et al.*, 2015). Importantly, further longitudinal studies should explore the ability of cortical mean diffusivity to predict disease progression at the single-subject level. Additionally, our study is the first to report the potential added value of cortical diffusion tensor imaging changes over cortical thickness in bvFTD. Further studies could explore the added value of the combined study of white and grey matter diffusion tensor imaging changes to improve pathological predictions (McMillan *et al.*, 2014; Downey *et al.*, 2015). All the aforementioned points are key aspects for candidate selection in clinical trials once protein-specific targeted therapies become available (Elahi and Miller, 2017).

The main strengths of this study are the relatively large number of bvFTD participants at a mild-to-moderate disease stage, and the surface-based analyses using a previously validated technique. This surface-based approach

solves some of the limitations and methodological concerns that have been previously reported when using a voxel-based approach (Coalson *et al.*, 2018). Moreover, we enriched our description of the cortical mean diffusivity in the bvFTD with established clinical measures of disease severity and CSF biomarkers. This study also has some limitations. First, we acknowledge that a substantial proportion of the bvFTD cases (38.6%) were excluded due to segmentation or diffusion tensor imaging processing errors. Even though this is an inherent limitation of our surface-based approach, future improvements in T_1 MRI acquisitions or the use of higher field MRIs, together with software improvements will likely reduce the number of subjects excluded due to segmentation errors. Of note, we observed that the excluded patients belonged to the probable bvFTD group (77.3% of the excluded cases) and were at a more advanced disease stage, as measured by the FTLD-CDR. Notwithstanding, cortical mean diffusivity may still provide valuable topographical information regarding the earliest cortical microstructural changes in patients at very mild disease stages (for example, sporadic bvFTD cases without overt cortical atrophy or even genetic cases) where fewer segmentation errors are expected to occur. Second, it could be argued that there may be confounding results related to the different acquisition protocols across centres. However, the results presented in the current study were obtained after using a validated state-of-the-art algorithm to harmonize diffusion data between centres (Fortin *et al.*, 2017; Montal *et al.*, 2017). Moreover, results were similar when analysing each centre independently regardless of the use of different diffusion weighted imaging sequences. Third, although we provide cross-sectional evidence that cortical mean diffusivity changes may be a novel sensitive metric to reflect neurodegeneration, further longitudinal studies and using presymptomatic mutation carriers should confirm that cortical mean diffusivity changes antedate cortical atrophy in patients with bvFTD. Fourth, because most of the included bvFTD cases did not have neuropathological evaluation, misdiagnosis could have occurred, especially in the possible bvFTD group. However, a high proportion of cases were found to have an increased certainty of underlying frontotemporal lobar degeneration when considering the available clinical, genetic and neuropathological information. Finally, as neuropathological evaluation was not available in most cases, we were not able to explore the precise pathological correlates of the observed cortical mean diffusivity changes.

In summary, this study supports the use of cortical mean diffusivity as a valuable novel biomarker for the cortical mapping of neurodegeneration-related microstructural changes in bvFTD. Further longitudinal studies in different populations including preclinical mutation carriers are needed to fully determine the diagnostic and prognostic utility of this biomarker, particularly at the earliest stages of the disease.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

Agosta F, Galantucci S, Magnani G, Marcone A, Martinelli D, Antonietta Volontè M, et al. MRI signatures of the frontotemporal lobar degeneration continuum. Hum Brain Mapp 2015; 36: 2602–14.

Alcolea D, Carmona-Iragui M, Suárez-Calvet M, Sánchez-Saudinós MB, Sala I, Antón-Aguirre S, et al. Relationship between β-secretase, inflammation and core cerebrospinal fluid biomarkers for Alzheimer's disease. J Alzheimers Dis 2014; 42: 157–67.

Alcolea D, Martínez-Lage P, Sánchez-Juan P, Olazarán J, Antúnez C, Izagirre A, et al. Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 2015; 85: 626–33.

Alcolea D, Vilaplana E, Suárez-Calvet M, Illán-Gala I, Blesa R, Clarimon J, et al. CSF sAPPβ, YKL-40, and neurofilament light in frontotemporal lobar degeneration. Neurology 2017; 89: 178–88.

Balasa M, Gelpi E, Martín I, Antonell A, Rey MJ, Grau-Rivera O, et al. Diagnostic accuracy of behavioral variant frontotemporal dementia consortium criteria (FTDC) in a clinicopathological cohort. Neuropathol Appl Neurobiol 2015; 4: 882–92.

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet 2015; 386: 1672–82.

Bejanin A, La Joie R, Landeau B, Belliard S, La Sayette de V, Eustache F, et al. Distinct interplay between atrophy and hypometabolism in Alzheimer's versus semantic dementia. Cereb Cortex 2018. doi: 10.1093/cercor/bhy069.

Binney RJ, Pankov A, Marx G, He X, McKenna F, Staffaroni AM, et al. Data-driven regions of interest for longitudinal change in three variants of frontotemporal lobar degeneration. Brain Behav 2017; 7: e00675.

Brettschneider J, Del Tredici K, Irwin DJ, Grossman M, Robinson JL, Toledo JB, et al. Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). Acta Neuropathol 2014; 127: 423–39.

Chare L, Hodges JR, Leyton CE, McGinley C, Tan RH, Kril JJ, et al. New criteria for frontotemporal dementia syndromes: clinical and pathological diagnostic implications. J Neurol Neurosurg Psychiatry 2014; 85: 865–70.

Coalson TS, Van Essen DC, Glasser MF. The impact of traditional neuroimaging methods on the spatial localization of cortical areas. Proc Natl Acad Sci U S A 2018; 115: E6356–65.

Davies RR, Kipps CM, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Progression in frontotemporal dementia: identifying a benign behavioral variant by magnetic resonance imaging. Arch Neurol 2006; 63: 1627–31.

Devenney E, Forrest SL, Xuereb J, Kril JJ, Hodges JR. The bvFTD phenocopy syndrome: a clinicopathological report. J Neurol Neurosurg Psychiatry 2016; 87: 1155–6.

Devenney E, Swinn T, Mioshi E, Hornberger M, Dawson KE, Mead S, et al. The behavioural variant frontotemporal dementia phenocopy syndrome is a distinct entity—evidence from a longitudinal study. BMC Neurol 2018; 18: 56.

Downey LE, Mahoney CJ, Buckley AH, Golden HL, Henley SM, Schmitz N, et al. White matter tract signatures of impaired social cognition in frontotemporal lobar degeneration. Neuroimage Clin 2015; 8: 640–51.

Elahi FM, Marx G, Cobigo Y, Staffaroni AM, Kornak J, Tosun D, et al. Longitudinal white matter change in frontotemporal dementia subtypes and sporadic late onset Alzheimer's disease. Neuroimage Clin 2017; 16: 595–603.

Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol 2017; 13: 457–76.

Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000; 97: 11050–5.

Fortin J-P, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, et al. Harmonization of multi-site diffusion tensor imaging data. NeuroImage 2017; 161: 149–70.

Ganepola T, Nagy Z, Ghosh A, Papadopoulo T, Alexander DC, Sereno MI. Using diffusion MRI to discriminate areas of cortical grey matter. NeuroImage 2018; 182: 456–68.

Gómez-Tortosa E, Serrano S, de Toledo M, Pérez-Pérez J, Sainz MJ. Familial benign frontotemporal deterioration with C9ORF72 hexanucleotide expansion. Alzheimers Dement 2014; 10: S284–9.

Gossink FT, Dols A, Kerssens CJ, Krudop WA, Kerklaan BJ, Scheltens P, et al. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. J Neurol Neurosurg Psychiatry 2016; 87: 64–8.

Hagler DJ, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. NeuroImage 2006; 33: 1093–103.

Illán-Gala I, Alcolea D, Montal V, Dols-Icardo O, Muñoz L, De Luna N, et al. CSF sAPPβ, YKL-40, and NfL along the ALS-FTD spectrum. Neurology 2018; 91: e1619–28.

Irwin DJ, Brettschneider J, McMillan CT, Cooper F, Olm C, Arnold SE, et al. Deep clinical and neuropathological phenotyping of Pick disease. Ann Neurol 2016; 79: 272–87.

Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, Fong JC, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. J Neurol Neurosurg Psychiatry 2012; 83: 358–64.

Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131: 2957–68.

La Joie R, Perrotin A, Barré L, Hommet C, Mézenge F, Ibazizene M, et al. Region-specific hierarchy between atrophy, hypometabolism, and β-amyloid (Aβ) load in Alzheimer's disease dementia. J Neurosci 2012; 32: 16265–73.

Lam BYK, Halliday GM, Irish M, Hodges JR, Piguet O. Longitudinal white matter changes in frontotemporal dementia subtypes. Hum Brain Mapp 2013; 35: 3547–57.

Landqvist Waldö M, Frizell Santillo A, Passant U, Zetterberg H, Rosengren L, Nilsson C, et al. Cerebrospinal fluid neurofilament light chain protein levels in subtypes of frontotemporal dementia. BMC Neurol 2013; 13: 54.

Llamas-Velasco S, García-Redondo A, Herrero-San Martín A, Puertas Martín V, González- Sánchez M, Pérez-Martínez DA, et al. Slowly progressive behavioral frontotemporal dementia with C9orf72 mutation. Case report and review of the literature. Neurocase 2018; 24: 68–71.

Lleo A, Irwin DJ, Illán-Gala I, McMillan CT, Wolk DA, Lee EB, et al. A 2-step cerebrospinal algorithm for the selection of frontotemporal lobar degeneration subtypes. JAMA Neurol 2018; 75: 738–45.

Mahoney CJ, Ridgway GR, Malone IB, Downey LE, Beck J, Kinnunen KM, et al. Profiles of white matter tract pathology in frontotemporal dementia. Hum Brain Mapp 2014a; 35: 4163–79.

Mahoney CJ, Simpson IJA, Nicholas JM, Fletcher PD, Downey LE, Golden HL, et al. Longitudinal diffusion tensor imaging in frontotemporal dementia. Ann Neurol 2014b; 77: 33–46.

McMillan CT, Avants BB, Cook P, Ungar L, Trojanowski JQ, Grossman M. The power of neuroimaging biomarkers for screening frontotemporal dementia. Hum Brain Mapp 2014; 35: 4827–40.

Meeter LH, Dopper EG, Jiskoot LC, Sánchez-Valle R, Graff C, Benussi L, et al. Neurofilament light chain: a biomarker for genetic frontotemporal dementia. Ann Clin Transl Neurol 2016; 3: 623–36.

Meeter LH, Kaat LD, Rohrer JD, van Swieten JC. Imaging and fluid biomarkers in frontotemporal dementia. Nat Rev Neurol 2017; 19: 109–419.

Menke RAL, Gray E, Lu C-H, Kuhle J, Talbot K, Malaspina A, et al. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. Ann Clin Transl Neurol 2015; 2: 748–55.

Montal V, Vilaplana E, Alcolea D, Pegueroles J, Pasternak O, Gonzalez-Ortiz S, et al. Cortical microstructural changes along the Alzheimer's disease continuum. Alzheimers Dement 2017; 14: 340–51.

Papma JM, Jiskoot LC, Panman JL, Dopper EG, Heijer den T, Donker Kaat L, et al. Cognition and gray and white matter characteristics of presymptomatic C9orf72 repeat expansion. Neurology 2017; 89: 1256–64.

Parker TD, Slattery CF, Zhang J, Nicholas JM, Paterson RW, Foulkes AJM, et al. Cortical microstructure in young onset Alzheimer's disease using neurite orientation dispersion and density imaging. Hum Brain Mapp 2018; 39: 3005–17.

Perry DC, Brown JA, Possin KL, Datta S, Trujillo A, Radke A, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. Brain 2017; 140: 3329–45.

Pijnenburg YAL, Verwey NA, van der Flier WM, Scheltens P, Teunissen CE. Discriminative and prognostic potential of cerebrospinal fluid phosphoTau/tau ratio and neurofilaments for frontotemporal dementia subtypes. Alzheimers Dement (Amst) 2015; 1: 505–12.

Ranasinghe KG, Rankin KP, Pressman PS, Perry DC, Lobach IV, Seeley WW, et al. Distinct subtypes of behavioral variant frontotemporal dementia based on patterns of network degeneration. JAMA Neurol 2016; 73: 1078–88.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134: 2456–77.

Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 2015; 14: 253–62.

Rohrer JD, Woollacott IOC, Dick KM, Brotherhood E, Gordon E, Fellows A, et al. Serum neurofilament light chain protein is a measure of disease intensity in frontotemporal dementia. Neurology 2016; 87: 1329–36.

Scherling CS, Hall T, Berisha F, Klepac K, Karydas A, Coppola G, et al. Cerebrospinal fluid neurofilament concentration reflects disease severity in frontotemporal degeneration. Ann Neurol 2014; 75: 116–26.

Schroeter ML, Laird AR, Chwiesko C, Deuschl C, Schneider E, Bzdok D, et al. Conceptualizing neuropsychiatric diseases with multimodal data-driven meta-analyses—the case of behavioral variant frontotemporal dementia. Cortex 2014; 57: 22–37.

Seo SW, Thibodeau M-P, Perry DC, Hua A, Sidhu M, Sible I, et al. Early vs late age at onset frontotemporal dementia and frontotemporal lobar degeneration. Neurology 2018; 90: e1047–56.

Tartaglia MC, Sidhu M, Laluz V, Racine C, Rabinovici GD, Creighton K, et al. Sporadic corticobasal syndrome due to FTLD-TDP. Acta Neuropathol 2010; 119: 365–74.

Weston PSJ, Simpson IJA, Ryan NS, Ourselin S, Fox NC. Diffusion imaging changes in grey matter in Alzheimer's disease: a potential marker of early neurodegeneration. Alzheimers Res Ther 2015; 7: 47.

Whitwell JL, Avula R, Senjem ML, Kantarci K, Weigand SD, Samikoglu A, et al. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. Neurology 2010; 74: 1279–87.

Wilke C, Preische O, Deuschle C, Roeben B, Apel A, Barro C, et al. Neurofilament light chain in FTD is elevated not only in cerebrospinal fluid, but also in serum. J Neurol Neurosurg Psychiatry 2016; 87: 1270–2.

Wood EM, Falcone D, Suh E, Irwin DJ, Chen-Plotkin AS, Lee EB, et al. Development and validation of pedigree classification criteria for frontotemporal lobar degeneration. JAMA Neurol 2013; 70: 1411–7.

Zhu T, Hu R, Qiu X, Taylor M, Tso Y, Yiannoutsos C, et al. Quantification of accuracy and precision of multi-center DTI measurements: a diffusion phantom and human brain study. NeuroImage 2011; 56: 1398–411.