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GREY AND WHITE MATTER BRAIN NETWORK CHANGES IN FRONTOTEMPORAL DEMENTIA SUBTYPES

Tim Nguyen[1,2],
Maxime Bertoux[3],
Claire O'Callaghan[1,2],
Samrah Ahmed[4],
John R. Hodges[1,2],
Michael Hornberger[1,2,5] *

[1]*Neuroscience Research Australia, Sydney, Australia*
[2]*School of Medical Sciences, University of New South Wales, Sydney, Australia*
[3]*Institut Jean Nicod, Ecole Normale Supérieure, Paris*
[4]*Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK*
[5]*Department of Clinical Neurosciences, Cambridge University, Cambridge, UK*

Abstract

Background: Frontotemporal dementia (FTD) comprises of three clinical syndromes, behavioural-variant frontotemporal dementia (bvFTD), semantic dementia (SV-PPA), and progressive nonfluent aphasia (NFV-PPA) with unique underlying neuroanatomical deficits. To date, however, grey matter structural differences and their connecting white matter tracts in this network have been mostly characterised in comparison to controls, whereas within FTD subtype comparisons in the same patients have not been explored.

Methodology: In 94 participants, including bvFTD (n = 16), SV-PPA (n = 16) and NFV-PPA (n = 16), as well as an age-matched control group (n = 46), we employed voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) to examine grey and white matter key signatures in each of the three FTD subtypes.

Results: Our results showed that bvFTD had specific ventromedial prefrontal cortex and striatum grey matter atrophy along with their connecting white matter tracts compared to other FTD subtypes. By contrast, SV-PPA showed additional temporal pole grey matter damage to bvFTD and grey and white matter temporal, amygdala and insula changes compared to NFV-PPA. Finally, NFV-PPA showed mild insula grey and white matter changes compared to bvFTD but differed from SV-PPA only on anterior corpus callosum white matter changes.

Conclusions: Our findings clearly indicate that not only grey matter regions of the FTD network but also their white matter connecting tracts have specific signatures for each FTD subtype. These promising findings highlight how neural network approaches can shed new light on neurodegenerative conditions and FTD in particular, which will inform future diagnostic and disease management.

Keywords

• Frontotemporal dementia • VBM • DTI • bvFTD • SV-PPA • NFV-PPA

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Introduction

Frontotemporal dementia (FTD) is the most common cause of early-onset dementia (age <65) after Alzheimer's disease (AD) [1,2]. Clinically, FTD is divided into three subtypes: two language variants (a non-fluent variant [NFV-PPA] and a semantic variant [SV-PPA] also known as semantic dementia) and a behavioural variant (bvFTD) [3]. All three subtypes manifest distinct clinical and imaging features at presentation, which merge as the disease progresses.

Grey matter structural neuroimaging studies in bvFTD have shown symmetrical or predominantly right-sided atrophy of the ventromedial prefrontal cortex (VMPFC) early in the course of the disease as well involvement of the insula, temporal pole, anterior cingulate, striatum and amygdala compared to age-matched controls which increases as the disease progresses [4-9]. Subcortical atrophy is also emerging as a major component of bvFTD with bilateral involvement of the striatum, specifically the caudate and putamen, and the thalamus [10]. While less investigated, changes in white matter tracts have also been identified in bvFTD patients, particularly involving tracts connecting regions of atrophy such as the genu of the corpus callosum (GCC) and the anterior superior longitudinal fasciculus (SLF). Additionally, the uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF) are also involved [11,12], thus revealing a comprehensive network of frontotemporal white matter damage in bvFTD.

In SV-PPA voxel-based morphometry (VBM) grey matter studies show a consistent pattern of focal bilateral temporal lobe atrophy in comparison to controls, which usually predominates in the left hemisphere, with the temporal pole and anterior fusiform gyrus being particularly affected [13]. In addition to these polar regions, the amygdala, anterior hippocampus, entorhinal cortex, are also commonly affected [14-16]. Other reports also highlight atrophy of extra-temporal regions, such VMPFC, anterior cingulate and insular cortices, particularly in the more advanced stages [2,17]. Subcortical grey matter atrophy is mainly circumscribed to the caudate nucleus [18]. In keeping with the grey matter findings, white matter tracts within the temporal lobes are consistently affected with significant changes identified in the inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UNC) [19]. Involvement of white matter tracts connecting temporal lobes to other cortical and subcortical regions have been also reported, such as in the anterior superior longitudinal fasciculus (SLF), arcuate fasciculus and genu of the corpus callosum [11,20].

* *E-mail: mh755@medschl.cam.ac.uk*

Finally, NFV-PPA is characterised by asymmetrical grey matter with greater involvement of the left hemisphere [21], with atrophy focused around the left inferior frontal cortex and insula [22-24] compared to controls. More recent studies show hypometabolism and atrophy centred on the left anterior region of the insula specifically [25]. Nevertheless, NFV-PPA can also present with more dorsal prefrontal as well as anterior parietal lobe changes, and striatal caudate atrophy [2,18]. The superior longitudinal fasciculus (SLF) tract undergoes the most severe changes in specifically the anterior part descending into the inferior frontal lobes and the posterior part descending into the posterior temporal lobe [11]. Dysfunction to the arcuate fasciculus is also commonly observed [11,26,27].

In the light of these structural grey and white matter results, it becomes evident that FTD subtypes show unique and shared grey and white matter patterns when compared to healthy participants. Importantly, however, the vast majority of the reviewed studies conducted their grey and white matter analysis in separate patient cohorts, which makes it difficult to explore the correspondence between grey and white matter changes in the FTD spectrum. To our knowledge no study, to date, has contrasted directly grey and white matter changes across FTD subtypes in the same patients to establish more definitively the areas of common and unique patients [cf. 28].

The current study addresses this point directly by investigating grey and white matter integrity in the same patients of three clinical FTD subtypes in comparison with matched-controls focusing the analyses on the key regions (amygdala, insula, VMPFC, striatum, temporal pole) that have been described to be involved in FTD atrophy as well as their connecting tracts. We predict that FTD subtypes will show classic patterns of atrophy and white matter degeneration compared to controls as previously reported. We also predict that comparing within FTD subtypes will reveal unique grey and white matter network differences, in particular bvFTD should show more VMPFC, SV-PPA more temporal pole and NFV-PPA more insula changes.

Experimental procedures

Case selection

A total of 94 participants took part in this study. Patients were ascertained from the FTD Research Clinic, FRONTIER, in Sydney Australia, resulting in a sample of 16 bvFTD, 16 SV-PPA and 16 NFV-PPA patients, and 46 controls. All FTD patients met current consensus criteria for bvFTD, NFV-PPA or SV-PPA [29,30], showing the progressive behavioural and/or language decline characteristic of FTD. Those with logopenic variant PPA were excluded. Patients also met criteria of evidence of atrophy localised to frontal and/or temporal lobes via MRI. A group of 46 healthy adults were included as controls. Groups were matched for age, gender, and education. Testing and scanning was conducted at the first clinic visit of each patient.

Ethics statement

This study followed the principles outlined in the Declaration of Helsinki and ethics approval was obtained from the Human Research Ethics Committee of South Easter Sydney/Illawarra Area Health Service (HREC 10/126). The authors declare no conflicts of interest.

Test selection

The Addenbrooke's Cognitive Examination Revised (ACE-R) and the Cambridge Behavioural Inventory Revised (CBI-R) were testing methods employed on the basis of their high sensitivity, specificity and feasibility. The ACE-R detects early cognitive impairment with 94% sensitivity and 89% specificity. The patient works through a battery of items designed to reveal levels of functioning across five subscales: attention & orientation, memory, fluency, language and visuospatial cognition. The total possible score is 100, with higher scores denoting better preserved cognitive abilities. Scores below 88 are indicative of cognitive impairment (Mioshi et al., 2006).

The CBI-R is a 45-item carer questionnaire mapping the neuropsychiatric topography of the patient and its material impacts in daily life. Each item, a given behaviour, is ascribed a frequency rating (0-4) – 0 indicating no impairment, 1 a rare occurrence (a few instances per month), 2 a repeated occurrence (a few instances per week), 3 a daily occurrence, and 4 a constant occurrence. The CBI-R stands corroborated by the Neuropsychiatric Inventory (NPI) as an effective measure of neuropsychiatric symptoms in neurodegenerative conditions (Wedderburn et al., 2008). The maximum score is 180, signifying absolute behavioural and psychological dysfunction (Results are reported herein as percentages, for simplicity). Thus higher scores in CBI-R indicate greater impairment, in contrast with grading of ACE-R scores.

Imaging acquisition

Patients and controls were scanned on a 3 T Philips MRA scanner. T1-weighted acquisition: coronal orientation, matrix 256x256, 200, 1x1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TI = 2.6/5.8 ms.

DTI-weighted acquisition: 32 gradients, TR/TE/TI: 8400/68/90 ms, b-value = 1000 s/mm^2, 55 2.5-mm horizontal slices, end resolution: 2.5x2.5x2.5 mm^3, 96x96 matrix; repeated 2 times. Note: DTI scans were not available in two FTD patients.

Voxel-based morphometry (VBM) analysis

Voxel based morphometry was conducted on the three dimensional T1-weighted scans using the FLS-VBM toolbox in the FMRIB software library package (http://ww.fmrib.ox.ac.uk/fsl/).

In a first step, brain extraction was performed on all scans using the BET algorithm [31] in FSL using a fractional intensity threshold of 0.22. Brain extraction was checked visually for all scans so that no brain matter was excluded. Similarly, the scans were checked for whether any non-brain matter (e.g. skull, dura mater, optic nerve) were still present in the brain extracted images. If non-brain matter was visually detected or brain matter was falsely excluded, the BET algorithm for the scan was repeated by changing the fractional intensity threshold to give smaller or larger brain outline estimates. A study-specific grey matter template was then created by including 10 scans of each group (total n = 40). The same number of scans across groups was used to avoid any bias during the registration step (i.e. favouring

one group) while at the same time representing all included groups equally. The template scans were then registered to the Montreal Neurological Institute Standard space (MNI 152) using non-linear *b-spline* representation of the registration warp field resulting in study-specific grey matter template at 2x2x2 mm^3 resolution in standard space. At the same time, all brain extracted scans were also processed with the FMRIB's Automatic Segmentation Tool (FAST v4.0) [32] to achieve tissue segmentation of i) grey matter, ii) white matter and iii) CSF via a hidden Markov random field model and an associated Expectation-Maximization algorithm. The FAST algorithm also corrected for spatial intensity variations such as bias field or radio-frequency inhomogeneities in the scans, resulting in partial volume maps of the scans. In a next step, the grey matter partial volume maps were then non-linearly registered to the study-specific template via non-linear *b-spline* representation of the registration warp and were modulated by dividing them by the Jacobian of the warp field to correct for the contraction/enlargement due to the non-linear component of the transformation [33]. Finally, the normalised and modulated grey matter maps were smoothed with an isotropic Gaussian kernel (standard deviation = 3 mm; full width half maximum = 8 mm).

Based on the reviewed literature in the introduction, we created a regions of interest (ROI) mask for the grey and white matter analyses. Regions included were taken from the Harvard-Oxford probabilistic grey and white matter atlases as follows: VMPFC (frontomedial cortex, subcallosal area, anterior cingulate gyrus and orbitofrontal cortex); insula; amygdala; temporal pole; striatum (caudate, putamen, pallidum and nucleus accumbens).

The statistical analysis was performed by employing a voxel-wise general linear model. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method [34]. The TFCE method is a cluster-based thresholding method which does not require the setting of an arbitrary cluster forming threshold (e.g. t,z<4), instead it takes a raw statistics image and produces an output image in which the voxel-wise values represent the amount of cluster-like local spatial support. The TFCE image is then turned into voxel-wise p-values via permutation testing. We employed a permutation-based non-parametric testing with 5000 permutations [35]. All patient vs. control comparisons are reported at $p < 0.05$ after Family-wise Error (FWE) correction, all within-patient were tested at a significance level of $p < 0.001$, uncorrected and a cluster threshold of 20 contiguous voxels.

Diffusion tensor imaging (DTI) analysis

In a first step, the two DTI sequences were averaged for each participant, visually checked for field inhomogeneity distortions. They were further corrected for eddy current distortions (i.e. stretches and shears induced by the gradient coils during image acquisition) by using affine registration to the b0 reference volume.

The diffusion tensor models were then fitted at each voxel via the FDT toolbox in FSL (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html), resulting in maps for three eigenvalues (L1, L2, L3), which allowed calculations of fractional anisotropy (FA) maps for each subject. FA maps for all subjects were visually checked to identify errors in the fitting of the eigenvalues. In particular, corpus callosum, corticospinal tract and inter-hemispheric commissure were visually checked for fibre orientation information as they have some of the most consistent white matter orientations in the brain. Tract-based spatial statistics (TBSS) [36] from FSL were used to perform a skeleton-based analysis of white matter FA. FA maps of each individual subject were nonlinear co-registered using FNIRT [33,37] to the MNI standard space of the FMRIB58_FA template and were visually checked for any registration errors. The template was subsampled at 1x1x1 mm^3 due to the coarse resolution of native DTI data (i.e. 2.5x2.5x2.5 mm^3). After image registration, FA maps were averaged to produce a group mean FA image. A skeletonization algorithm [36] was applied to the group mean FA image to define a group template of the lines of maximum FA, assumed to correspond to centres of white matter tracts. The resulting binary skeleton mask defines the set of voxels used in all subsequent processing. Next a distance map is created from the skeleton mask. FA values for each individual subject were then projected onto this group template skeleton.

Once again, to analyse only the ROI, we created a white matter mask consisting of the frontomedial cortex, subcallosal area, anterior cingulate gyrus and orbitofrontal cortex, making up the ventromedial prefrontal cortex (VMPFC); insular; amygdala; temporal pole; and caudate, putamen, pallidum and nucleus accumbens, making up the striatum. The connecting tracts between these regions were also included.

Similar to the VBM analysis, the skeletonized FA data was then statistically tested via a voxel-wise general model. Significant clusters were formed by employing the threshold-free cluster enhancement (TFCE) method as described in the VBM analysis. Clusters were tested using permutation-based non-parametric testing with 5000 permutations. Like the VBM analysis, all patient vs. control comparisons are reported at $p < 0.05$ after Family-wise Error (FWE) correction, all within-patient were tested at a significance level of $p < 0.001$, uncorrected and a cluster threshold of 20 contiguous voxels. The overlap analyses for the VBM and DTI data were created by a multiplication of the contrasts, which resulted in inclusive or overlap masks across groups.

Results

Demographics

No significant differences were identified for any of the demographic variables (age, gender and education) across patient groups and the control cohort ($p > 0.1$) (Table 1). Importantly, disease duration did not differ between the bvFTD, SV-PPA and NFV-PPA groups ($p > 0.1$).

Voxel-based morphometry and DTI analysis

Control comparisons

As can be seen in Figure 1, bvFTD patients showed the well-known severe grey matter atrophy bilaterally involving the ventromedial prefrontal cortex (VMPFC), insular, temporal pole and amygdala. The right striatum also had severe grey matter atrophy, whereas the

Table 1. Comparison of demographics across bvFTD, SV-PPA, NFV-PPA and Control.

Demographics	bvFTD	SV-PPA	NFV-PPA	Controls
N	16	16	16	46
Age (mean, SD) years	61.86 (9.92)	61.48 (6.52)	66.75 (9.51)	65.92 (6.09)
Sex (M/F)	10/6	11/5	9/7	21/25
Education (mean, SD) years	11.73 (2.74)	12.81 (3.55)	13.03 (2.72)	12.56 (2.35)
Disease duration (mean, SD years	3.93 (1.84)	4.09 (1.30)	3.89 (2.29)	0.00 (0.00)

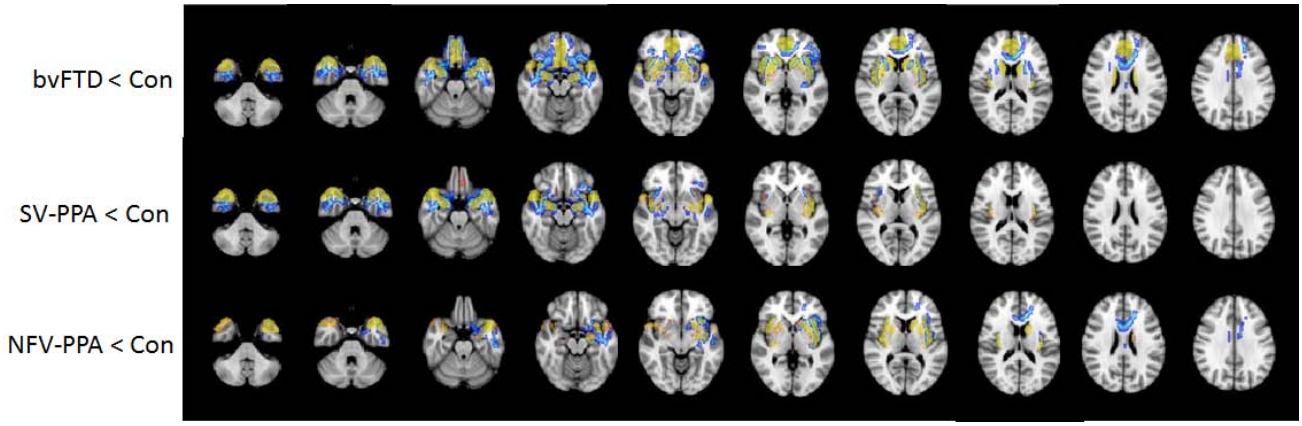

Figure 1. Figure shows the voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) findings for: bvFTD vs. controls; SV-PPA vs. controls and NFV-PPA vs. controls. VBM findings are shown in red-yellow; DTI findings are shown in light-dark-blue. Coloured voxels show regions that were significant in the analysis at $p < 0.05$ family-wise error (FEW) corrected. All clusters reported $t > 3.50$. Clusters are overlaid on the MNI standard brain.

left was less affected. White matter tracts were similarly affected within and between all regions of interest.

SV-PPA patients had severe grey matter atrophy involving the temporal pole and amygdala, with the insula and striatum also affected, though to a lesser degree. Finally, the VMPFC showed very mild atrophy (Figure 1). White matter changes were convergent with these findings with amygdala and temporal pole regions showing severe DTI changes while insula and striatum showed moderate changes only. Interestingly, the right hemispheric insula was more affected than the left in SV-PPA.

Finally, NFV-PPA patients showed significant grey matter atrophy in bilateral insula (Figure 1). The striatum, temporal pole and amygdala also showed moderate atrophy, except for the right amygdala, which was only mildly affected. The VMPFC was virtually unaffected in NFV-PPA. White matter changes were focused on the left hemisphere with temporal lobe and insula connections most affected. Interestingly, there were also some striatal and particularly anterior corpus callosum changes for the DTI analysis.

Between patient group comparisons

Patient groups were contrasted with each other to investigate grey and white matter degeneration patterns specific to each clinical FTD subtype Figure 2, Figure 3 & Table 2.

SV-PPA vs. bvFTD

The SV-PPA group compared to bvFTD showed significantly more grey matter atrophy in bilateral temporal pole and amygdala regions, especially on the left hemisphere. The left striatum and insula showed more subtle changes, while the VMPFC was notably spared compared to bvFTD. Interestingly, there were virtually no additional white matter changes in SV-PPA compared to bvFTD, with the exception of subtle changes in left striatum and right corpus callosum.

By contrast, bvFTD patients had more atrophy of the VMPFC and striatum bilaterally compared to SV-PPA. The right insula was also moderately impaired whereas the left showed only mild changes compared to SV-PPA. The bvFTD group showed additionally more significant white matter changes than SV-PPA in VMPFC and striatal regions. Interestingly, the bvFTD patients did not have additional amygdala or temporal pole changes compared to SV-PPA.

NFV-PPA vs. SV-PPA

Contrasting NFV-PPA with SV-PPA revealed no regions of greater grey matter atrophy in NFV-PPA. By contrast, NFV-PPA had significantly more white matter changes in the anterior corpus callosum in particular, with more minor changes in other prefrontal cortex regions.

The reverse contrast revealed that the SV-PPA patients had significantly more atrophy in bilateral temporal pole and amygdala regions than NFV-PPA. No other grey matter regions were significant. White matter changes were mainly localised in temporal lobe regions, with an additional minor cluster in the right insula.

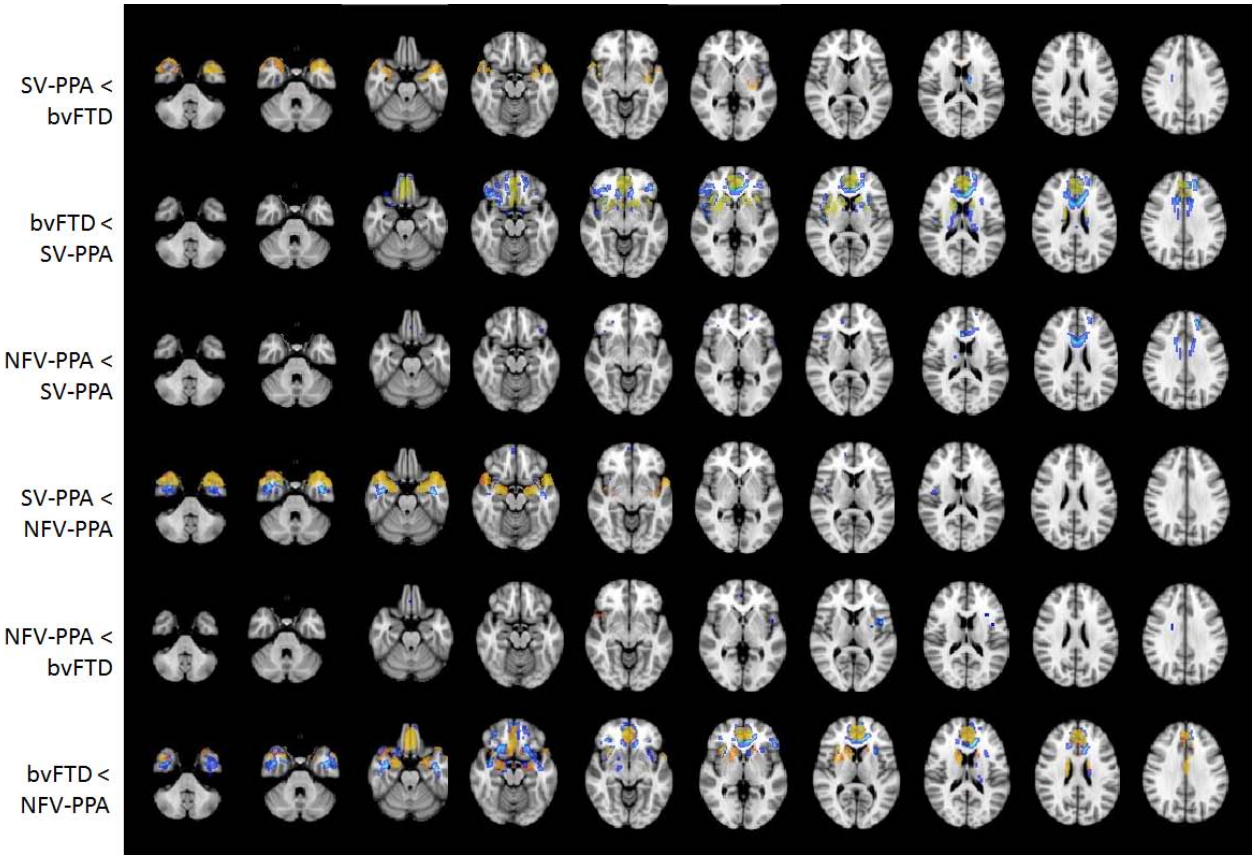

Figure 2. Figure shows the voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) findings for the within patient comparisons. VBM findings are shown in red-yellow; DTI findings are shown in light-dark-blue. Coloured voxels show regions that were significant in the analysis at $p < 0.001$ uncorrected. All clusters reported $t > 3.50$. Clusters are overlaid on the MNI standard brain.

NFV-PPA vs. bvFTD

Comparing NFV-PPA to bvFTD, there was greater grey matter atrophy of the anterior insula on the right in NFV-PPA only. Interestingly, however, white matter changes were significantly greater in NFV-PPA in the region of left insula.

Finally, bvFTD showed substantial more grey matter changes compared to NFV-PPA involving the VMPFC, striatum, amygdala and temporal pole. The insula by contrast was mostly spared. Similarly, substantial white matter changes were observed in the above regions and their connection with frontotemporal regions being particularly affected.

Table 2. Summary of grey and white matter findings. Rows indicate where each FTD subtype shows more grey and white matter changes compared to the other groups (columns).

	bvFTD	SV-PPA	NFV-PPA
bvFTD		VMPFC Striatum (R Insula)	VMPFC Temporal pole Amygdala Striatum
SV-PPA	Temporal pole L Insula		Temporal pole Amygdala L insula
NFV-PPA	R insula – grey L insula – white	VMPFC - white	

Discussion

Our study confirms that the clinical variants of FTD are characterised by distinctive profiles of grey and white matter involvement. The findings highlight the large overlap in grey and white matter change in clinical subtypes. There were however, changes that were specific to each clinical presentation. The unique role of the combined grey and white matter pathology of the anterior region in SV-PPA, and of the VMPFC in BV-FTD confirmed while, our study points to a more substantial role for subcortical white matter tract pathology in NFV-PPA than hitherto recognised

In more detail, all FTD patient subgroups showed significant changes compared to controls replicating previous findings. Particularly, bvFTD showed significant bilateral damage to the ventromedial prefrontal cortex (VMPFC), insular, temporal pole and amygdala, as well as in the underlying white matter tracts thus corroborating previous studies [4,6,7,37]. Similarly, the SV-PPA vs. controls contrast revealed greater involvement of the left hemisphere overall, with particularly the temporal pole, insula and amygdala, together with their underlying tracts being affected [2,13,16,38]. Finally, NFV-PPA exhibited the well-known insula changes [25,39], although we also found additional atrophy in bilateral temporal poles, left amygdala and left striatum. Interestingly, the white matter tract changes in NFV-PPA were not confined to the insula, instead there was additional involvement of striatal and VMPFC white matter tracts, in particular the anterior corpus callosum. This finding is intriguing, as it suggests a dissociation of grey and white matter integrity in NFV-PPA with some regions showing both changes (insula, striatum), while other regions show solely grey (temporal pole) or white matter (VMPFC) changes. This finding requires future investigation to delineate the contribution of these divergent grey and white matter changes the clinical symptomatology of NFV-PPA.

More importantly, the within- subtype comparisons revealed that bvFTD patients showed significantly more grey and white matter changes involving the VMPFC and striatum compared to SV-PPA and NFV-PPA. In addition, bvFTD showed significantly greater changes in the right insula compared to SV-PPA, although they were relatively subtle. Compared to NFV-PPA the bvFTD showed changes in temporal pole and amygdala regions. These findings further corroborate the specificity of the VMPFC [5] and striatum [40,41] in bvFTD. VMPFC changes, in particular in orbitofrontal and anterior cingulate cortices in bvFTD [42,43], that have been associated with many of the classical behavioural features in the disease, notably disinhibition, apathy, loss of insight and reduced empathy [44-46]. The striatal contributions to bvFTD symptomology are less well established,

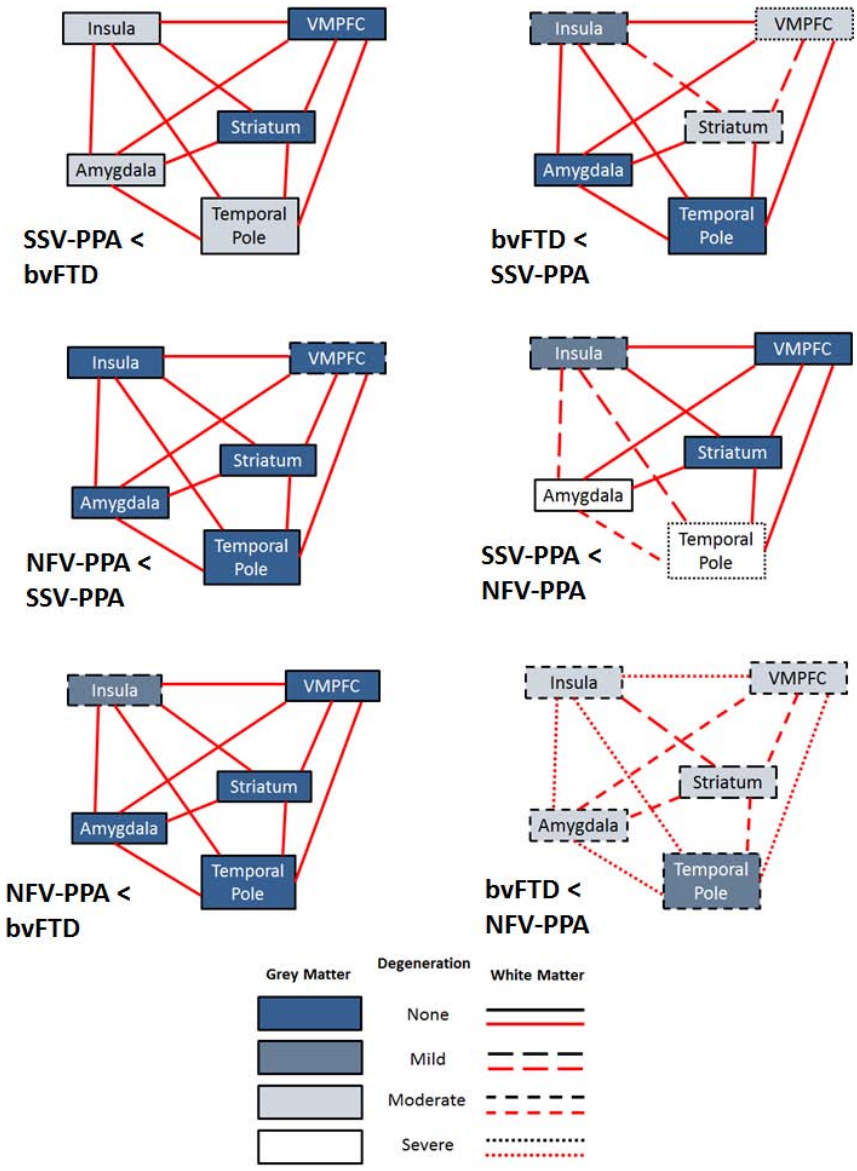

Figure 3. Figure shows a graphical interpretation of the main within-patient comparisons for the analysed regions and their connections. We classified the level of impairment (severe, moderate, mild, none) as follows: Severe = 75%+ of entire structure impaired; Moderate = 25-75% of entire structure impaired; Mild = less than 25% of entire structure impaired; None = no statistically significant ($p < 0.001$, uncorrected) impairment detected.

although this region is consistently affected in this FTD subtype [47]. Recent findings suggest that the striatal changes in bvFTD might be related to inhibitory and apathy processes [48]. The symptom overlap with VMPFC should be not surprising as the striatum, in particular its ventral part, has strong prefrontal cortex connections and thus frontostriatal interactions are likely to contribute to similar symptoms in the patients. Our finding of frontostriatal DTI changes in bvFTD compared to the other FTD subtypes dovetails with this notion, though the specific role of each region to the generation of symptoms in bvFTD remains unclear at this stage.

Comparisons between SV-PPA and the other FTD subtypes revealed that grey and white matter temporal pole changes are relatively specific to this group. This is unsurprising, as temporal pole grey matter atrophy has been

well documented as characteristic of SV-PPA and has directly been associated semantic knowledge deficits [49]. Nevertheless, the DTI white matter findings in this region revealed an interesting dissociation between SV-PPA and the other FTD subtypes, with SV-PPA showing significant white matter changes compared to NFV-PPA but not compared to bvFTD. This seems surprising as SV-PPA shows significantly more grey matter temporal pole changes although the two groups do not differ in the degree of white matter DTI changes. This finding would suggest that in bvFTD white matter pathology is more severe than grey matter changes and can affect the temporal pole to a similar degree as SV-PPA. An interesting question arising from this finding is whether these DTI changes have a role in the symptom genesis in bvFTD? Another interesting finding in SV-PPA was the additional grey matter atrophy in the left insula compared to NFV-PPA and bvFTD. The specific contributions of this atrophy remain unclear. Finally, SV-PPA showed virtually no striatal changes overall and compared to other FTD subtypes, suggesting that the striatum plays a minimal role in the symptomology of SV-PPA and could be potentially used as a diagnostic marker to distinguish SV-PPA from other FTD subtypes.

The changes found in the NFV-PPA group were mild compared to the other groups with the insula emerging as the signature region when compared to the other variants. The NFV-PPA differed from bvFTD only in insula integrity with an interesting differential lateralisation of grey and white matter changes. More specifically, grey matter changes were greater on the right, while there were more left insula white matter changes when compared to bvFTD. It is not clear why there should be a lateralisation of those grey and white changes. The insula is a complex multimodal region which is implicated in a multitude of processes in the healthy. Still, the finding of greater white matter tract pathology in NFV-PPA which is characterised by apraxia of speech and/or agrammatism [30] suggests that white tract pathology may play a greater role in the symptomatology than hitherto appreciated. The second contrast, comparing NFV-PPA and SV-PPA revealed no grey matter differences between both groups, but significantly more anterior corpus callosum changes in NFV-PPA. It is not clear why this region should be particularly affected in NFV-PPA as this FTD type does not usually have significant VMPFC atrophy, indeed even compared to controls NFV-PPA do not show VMPFC atrophy but only white matter changes. Future studies are needed to explore this interesting finding.

Our findings have clinical implications as they reveal specific and shared grey and white matter contributions across FTD subtypes. In particular, the VMPFC and striatum emerge as potential diagnostic neuroimaging markers for bvFTD as they reliably distinguish it from SV-PPA and NFV-PPA. As mentioned above VMPFC changes have been well described in bvFTD, however the contribution of striatal changes might further increase diagnostic accuracy for this group, in particular if there are convergent behavioural/cognitive measures available. Not surprisingly, our findings reinforced that the anterior temporal region is a critical neuroimaging marker of SV-PPA, although white matter changes in this region should be interpreted with caution as they also occur in the bvFTD subtype. Finally, concerning the language subtypes (SV-PPA, NFV-PPA) – which can sometimes be difficult to distinguish on language presentation alone – our current findings indicate that white matter tract pathology in the region of the insula and corpus callosum changes are indicative of NFV-PPA

Despite these promising findings, it would be important to replicate our within-FTD subtypes comparisons in independent patient samples. In addition, we did not have pathological confirmation in our patients to explore the relationship between pathological subtypes and patters of grey/white matter change *in vivo*. Future studies addressing these issues are needed, which could also investigate longitudinal grey and white matter changes in these key regions as well as exploring the diagnostic efficacy of the identified regions in de novo patients

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