Whole-Brain White Matter Disruption in Semantic and Nonfluent Variants of Primary Progressive Aphasia

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Abstract: Semantic (svPPA) and nonfluent (nfPPA) variants of primary progressive aphasia are associated with distinct patterns of cortical atrophy and underlying pathology. Little is known, however, about their contrasting spread of white matter disruption and how this relates to grey matter (GM) loss. We undertook a structural MRI study to investigate this relationship. We used diffusion tensor imaging, tract-based spatial statistics, and voxel-based morphometry to examine fractional anisotropy (FA) and directional diffusivities in nine patients with svPPA and nine patients with nfPPA, and compared them to 16 matched controls after accounting for global GM atrophy. Significant differences in topography of white matter changes were found, with more ventral involvement in svPPA patients and more widespread frontal involvement in nfPPA individuals. However, each group had both ventral and dorsal tract changes, and both showed spread of diffusion abnormalities beyond sites of local atrophy. There was a clear dissociation in sensitivity of diffusion tensor imaging measures between groups. SvPPA patients showed widespread changes in FA and radial diffusivity, whereas changes in

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axial diffusivity were more restricted and proximal to sites of GM atrophy. NfPPA patients showed isolated changes in FA, but widespread axial and radial diffusivity changes. These findings reveal the extent of white matter disruption in these variants of PPA after accounting for GM loss. Further, they suggest that differences in the relative sensitivity of diffusion metrics may reflect differences in the nature of underlying white matter pathology in these two subtypes. *Hum Brain Mapp* 34:973–984, 2013. © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Primary progressive aphasia (PPA) describes a group of neurodegenerative conditions marked by early selective language impairment (Mesulam, 2003). Recent work has characterized subtypes of PPA in terms of clinical and physiological hallmarks (Gorno-Tempini et al., 2004; Mesulam et al., 2009; Grossman, 2010; Rohrer et al., 2010a). The semantic variant of PPA (svPPA), also known as semantic dementia, presents with anomia and loss of single-word comprehension but with relatively fluent speech. Atrophy is typically asymmetric and usually most severe in the left anterior temporal lobe (Gorno-Tempini et al., 2004). Patients with the nonfluent variant (nfPPA) show effortful halting speech, and often agrammatism and/or apraxia of speech. Single-word comprehension is generally spared, though sentence comprehension is affected due to disrupted syntactic processing (Peelle et al., 2008). nfPPA is associated with atrophy of superior temporal, prefrontal, and insular regions (Nestor et al., 2003; Gorno-Tempini et al., 2004; Grossman, 2010; Whitwell et al., 2010). Although there is significant histopathologic heterogeneity at autopsy, both semantic and nonfluent variants are associated with frontotemporal degeneration-type pathology (Grossman, 2010).

Although recent work has characterized the atrophy patterns of PPA (Gorno-Tempini et al., 2004; Whitwell et al., 2010; Rohrer et al., 2010a), few studies to date have investigated the whole-brain pattern of white-matter abnormalities using diffusion tensor imaging (DTI), and none have compared this across different variants of PPA. Given the assumption that these syndromes reflect a breakdown of networks subsuming different aspects of language, it seems pertinent to ask whether they are associated with contrasting patterns of whole-brain white matter disruption. Examination of local changes in specific tracts of interest in PPA demonstrated disruption of a number of association fasciculi (Catani et al., 2003; Agosta et al., 2010; Whitwell et al., 2010; Galantucci et al., in press). svPPA may show more ventral involvement, including the uncinate, inferior longitudinal, and inferior fronto-occipital fasciculi (UF, ILF, IFOF) with relative sparing of dorsal tracts such as the superior longitudinal fasciculus (SLF) (Agosta et al., 2010; Whitwell et al., 2010). A recent study by Acosta-Cabronero et al. (2011) used a whole-brain voxel-

wise analysis in svPPA and found sparing of dorsal tracts. However, in a voxel-based morphometry (VBM) study of svPPA, Borroni et al. (2007) found involvement of voxels contributing to both ILF and SLF territories. Two studies have examined white matter in patients with nfPPA and found SLF involvement in set regions of interest (Whitwell et al., 2010) and in tractographic results (Galantucci et al., in press). The existing literature suggests there may be contrasting patterns of white matter involvement in PPA variants, but to our knowledge, no studies to date have examined whole-brain white matter abnormalities with DTI across different subtypes.

It is also pertinent to ask whether white matter changes have significance other than as a secondary outcome of grey matter (GM) atrophy in neurodegenerative disease. The importance of this issue is highlighted by recent work from Bosch et al. (2010). In a sample of patients with mild cognitive impairment or Alzheimer's disease, most of the white matter abnormalities in both groups were explained by global GM atrophy and vanished when this was accounted for. As such, DTI measures of white matter integrity may offer limited additional utility in some situations, but the relationship of GM loss to DTI changes has not been assessed in PPA.

We undertook a DTI study to examine whole-brain white matter diffusion differences in svPPA and nfPPA patients relative to controls. We used tract-based spatial statistics (TBSS) (Smith et al., 2006), a robust whole-brain DTI analysis method, and statistically accounted for total GM. Further, we related our findings descriptively to regional atrophy identified from VBM analysis of GM. In this way, we aimed to develop a cohesive picture of key whole brain white matter abnormalities in these PPA subtypes.

MATERIALS AND METHODS

Participants

Thirty-three patients with PPA were recruited from three behavioral neurology referral sites after clinical diagnosis by an experienced behavioral neurologist (S.E.B., D.T.-W., and T.C.). Nine patients were unable or unwilling to comply with scanning, and three were excluded due to

TABLE I. Participant characteristics

	svPPA	nfPPA	Control	
	(N = 9)	(N = 9)	(N = 16)	
	Mean (SD)	Mean (SD)	Mean (SD)	Group comparison
Sex	3 F	5 F	7 F	
Handedness	8 R	9 R	16 R	
Age	67.6 (7.6)	65.2 (10.8)	70.1 (8.7)	$F(2,34) = 0.3, P > 0.1$
Years of Education	17.9 (6.3)	15.8 (3.2)	17.1 (4.2)	$F(2,34) = 0.6, P > 0.1$
Years since first symptom	6.4 (2.7)	4.1 (2.0)	NA	$t(19) = 2.5, P = 0.06$
Fazekas Score (/3)	0.2 (0.4)	0.4 (0.5)	0.5 (0.3)	$F(2,32) = 0.94, P > 0.1$

diagnosis of mixed or logopenic PPA. Finally, three patients (two nfPPA and one svPPA) were excluded due to differences in diffusion imaging parameters. The remaining nine svPPA and nine nfPPA patients were age- and education-matched to each other and to 16 healthy controls.

All participants gave informed written consent prior to the study in accordance with the Declaration of Helsinki (see Anon, 1996). Study procedures were approved by the institutional research ethics boards of University of Toronto, the University Health Network, Sunnybrook Health Sciences Centre, the Centre for Addiction and Mental Health, and Baycrest.

Diagnosis was based on the clinical and radiological criteria outlined by Neary et al. (1998). In addition, the diagnosis of enrolled patients was later considered in light of recently proposed criteria (Gorno-Tempini et al., 2011). All svPPA patients additionally met the recently proposed criteria for the svPPA. They exhibited grammatically correct fluent speech, with clear word finding difficulties. All of the nfPPA patients exhibited effortful, halting speech with anomia. On formal testing, only two exhibited agrammatism in production and three had unequivocal apraxia of speech (i.e., distortions and speech sounds errors). None of the participants met criteria for logopenic variant PPA (Gorno-Tempini et al., 2011). Demographic data are listed in Table I.

Neuropsychological Assessment

Neuropsychological testing was completed for all participants. Formal language testing included the Boston Naming Test (Kaplan et al., 1983), Peabody Picture Vocabulary Test (Dunn and Dunn, 1997), the picture subtest of the Pyramids and Palm Trees (Howard and Patterson, 1992), reading of low-frequency regular and exception words (Patterson et al., 1994), the Test for Reception of Grammar (Bishop, 2003), and the repetition and aphasia quotient from the Western Aphasia Battery (Kertesz, 2007). Tests of general cognitive function included the Mini-mental Status Examination (MMSE; Folstein et al., 1975), the Montreal Cognitive Assessment (Nasreddine et al., 2005), and the

Dementia Rating Scale (Jurica et al., 2001). Visuospatial function tests included copy of the Rey-Osterreith Figure (Rey, 1941) and the Cube Analysis subtest from the Visual Object and Space Perception Battery (Warrington and James, 1991). Nonverbal reasoning was assessed with Ravens Colored Progressive Matrices (Raven, 1962). Table II lists the results of neuropsychological testing.

Image Acquisition

Scanning was completed on a 3.0T GE scanner with standard 8-channel headcoil, at Sunnybrook Health Sciences Centre at the University of Toronto. A three-dimensional T1-weighted image [repetition time (TR) 8.1ms, echo time (TE) 3.2ms, 256×192 matrix, 22 cm field of view (FOV), 1 mm slab thickness] and fluid-attenuated inversion recovery (FLAIR; TR 9300 ms, TE 140 ms, 256×192 matrix, 22 cm FOV, 3 mm slab thickness) image were first acquired. Diffusion weighted data were acquired using an 8-channel headcoil with array spatial sensitivity encoding technique parallel imaging factor of 2, along 23 noncollinear directions with a b value of 1000, and two unweighted images (TR 8800 ms, TE 80 ms, 128×128 matrix, 38 cm FOV, 3 mm slab thickness). Two one-NEX repetitions were collected for each participant.

Image Analysis

White matter disease

FLAIR images were reconstructed and examined for white matter hyperintensities. Most patients and controls had mild periventricular caps and a few punctate lesions. Visual ratings of severity (Fazekas et al., 1987) were assigned and are noted in Table I.

Total grey matter and voxel-based morphometry

T1-weighted images were brain-extracted using a semi-automated procedure based on intensities from a

TABLE II. Neuropsychological testing scores for each group

Test (maximum)*	svPPA, mean (SD)	nfPPA, mean (SD)	Control, mean (SD)
Language			
Boston Naming Test (/60)	9.9 (8.5) ^{a,b}	32.9 (21.3) ^a	55.4 (4.7)
Peabody Picture Vocabulary Test (/196)	72.7 (41.7) ^{a,b}	142.4 (55.8) ^a	192.0 (14.9)
Pyramids and Palm Trees-Pictures (/52)	40.3 (8.9) ^a	48.3 (2.9)	50.7 (0.8)
Reading—Low frequency regular words (/42)	31.4 (9.6) ^a	36.0 (13.8)	41.8 (0.6)
Reading—Low frequency exception words (/42)	17.8 (7.7) ^{a,b}	28.5 (11.0) ^a	38.8 (4.4)
Test for Reception of Grammar (/80)	60.6 (17.3) ^a	57.8 (17.6) ^a	78.3 (1.8)
Western Aphasia Battery—Repetition (/100)	79.1 (14.9) ^a	64.2 (31.7) ^a	98.9 (3.0)
Western Aphasia Battery—Aphasia Quotient (/100)	68.1 (18.1) ^a	73.3 (27.5) ^a	99.3 (0.8)
General cognitive function			
Mini-Mental State Examination (/30)	19.9 (8.4) ^a	20.0 (10.1) ^a	28.6 (1.0)
Montreal Cognitive Assessment (/30)	15.4 (7.4) ^a	15.1 (9.2) ^a	26.4 (2.4)
Dementia Rating Scale (/144)	99.2 (27.2) ^a	107.6 (35.7) ^a	142.1 (1.9)
Visuospatial			
Rey-Osterreith Figure Copy (/36)	29.5 (10.0)	25.6 (9.6) ^a	32.7 (1.4)
Visual Object and Space Perception Battery—Cube Analysis subtest (/10)	8.7 (2.9)	9.2 (1.0)	8.9 (2.0)
Non-verbal reasoning			
Ravens Colored Progressive Matrices (/36)	29.9 (8.5)	25.0 (8.2) ^a	32.3 (3.7)

*One-way analyses of variance revealed a significant ($P < 0.05$) effect of group on all tests except Cube Analysis. Posthoc Tukey's HSD tests:

^aSignificantly different from normal controls.

^bSignificantly different from nonfluent patients.

coregistered T2-weighted image, to ensure preservation of cerebrospinal fluid (CSF) and parenchyma (Kovacevic et al., 2002) and allow accurate calculation of total intracranial capacity (TIC). Segmentation of the resulting images was completed with FAST 4.1 (Zhang et al., 2001) (<http://www.fmrib.ox.ac.uk/analysis/research/fast/>) to derive GM partial volume images for each subject, used for both calculation of total GM volume (normalized by TIC), and VBM. For VBM processing, GM images from all nine svPPA, all nine nfPPA, and a random selection of nine control participants were nonlinearly aligned to Montreal Neurological Institute (MNI) standard space and averaged to form a template. All GM volumes were then nonlinearly aligned to this template, and divided by the jacobian of the warp field. These volumes were smoothed by 8 mm full-width-at-half-maximum and subjected to cross-subject statistics using nonparametric estimation in randomize (5,000 permutations; <http://www.fmrib.ox.ac.uk/fsl/randomise/>), with TIC and age as covariates of no interest (Douaud et al., 2009). The contrast of controls versus patients was examined, with a familywise error (FWE) corrected alpha of 0.05.

DTI preprocessing and TBSS analysis

DTI series were reconstructed, motion corrected, and averaged over repetitions. Following inspection for artifact, fractional anisotropy (FA), axial diffusivity (D_A), and radial diffusivity (D_R) maps were calculated using the diffusion toolbox (FDT) of FMRIB's software library (FSL;

<http://www.fmrib.ox.ac.uk/analysis/research/fdt/>). FA, D_R , and D_A images for each participant were warped into MNI space and "skeletonized" following the standard TBSS protocol (Smith et al., 2006). Statistical contrasts compared each patient group to controls using randomize as above, and with age and normalized GM volume as covariates of no interest (see Supporting Information). Results were FWE corrected at alpha of 0.05, with threshold-free cluster enhancement. Investigation of tract territories was carried out by overlaying a probabilistic tractography atlas in standard space (Wakana et al., 2004; Hua et al., 2008).

RESULTS

Semantic Variant PPA

Fractional anisotropy

svPPA patients showed multiple areas of reduced FA compared to controls (Fig. 1). These were largely lateralized to the left hemisphere and included ventral regions contributing to the UF within the medial temporal and ventral frontal lobes, and the anterior portions of the IFOF and ILF projecting into the temporal pole. Dorsally, there was substantial involvement of the bilateral forceps minor, genu of the corpus callosum (CC), portions of left prefrontal white matter and left parieto-frontal white matter, contributing to the SLF and corona radiata. The right hemisphere showed changes limited to portions of the skeleton contributing to the UF and right SLF (Fig. 1, top panel). See Table III for a summary of DTI findings.

Figure 1.

DTI and VBM results from comparison of nine svPPA patients to 16 controls. Top row shows significant reductions in FA among patients in gold, overlaid with GM atrophy in blue. Second row shows D_A increases in green, third row D_R increases in red. Areas of white matter change distant from atrophy are highlighted (white arrows). All images thresholded at $P < 0.05$, FWE corrected. Abbreviations as in text. Left side of coronal and axial brain images is right hemisphere.

Axial diffusivity

Patients with svPPA showed significant increases in D_A . These were also left biased but included bilateral ventral portions contributing to the ILF and UF. The pattern of increased D_A largely overlapped areas of reduced FA ventrally, but dorsally showed minimal involvement, limited to the anterior thalamic projection (ATP) on the left (Fig. 1, middle panel).

Radial diffusivity

D_R increases were widespread. Ventrally, there was increased D_R in bilateral temporal and orbitofrontal

regions, reflecting involvement of UF, IFOF, and ILF territories. There was also involvement of the forceps minor and anterior limb of the internal capsule (IC) and/or ATP, and bilateral superior temporal white matter. In dorsal tracts, there was partial overlap with reduced FA in parieto-frontal SLF white matter within the left hemisphere, though D_R changes were more extensive, and included the left cingulum. No changes were seen in right hemisphere dorsal tracts (Fig. 1, bottom panel).

Voxel-based morphometry

svPPA patients showed significant atrophy in bilateral temporal regions, greatest on the left where it extended to

TABLE III. Summary of involved tract territories

	Association/limbic tracts				Callosal tracts				Projection tracts		
	Dorsal (SLF, AF, Cingulum)		Ventral (ILF, IFOF, UF)		Forceps Minor		Genu	Body	(ATP, IC)		
Metric	Left	Right	Left	Right	Left	Right				Left	Right
<i>svPPA</i>											
FA	X	X	X	X	X	X	X			X	
D_A			X	X						X	
D_R	X		X	X	X					X	X
<i>nfPPA</i>											
FA			X								
D_A	X	X	X	X	X	X	X	X	X	X	X
D_R	X	X	X	X	X	X	X	X	X	X	

involve posterior temporaloccipital regions inferiorly and the temporoparietal junction superiorly. Atrophy also included bilateral insula, inferior frontal, and medial frontal regions, precuneus, and medial temporal lobe. Subcortical involvement was seen in the left hemisphere, encompassing the putamen and accumbens nuclei (Fig. 1).

Correspondence of VBM and DTI changes

By overlaying TBSS and VBM results, we examined the spatial concordance of grey- and white-matter changes. The anterior temporal lobes were highly involved in both tissue types and all three metrics. However, FA and D_R changes extended more dorsally, into territories that were more distant from sites of grey-matter atrophy. FA changes in the right SLF region were also removed from GM loss.

Nonfluent Variant PPA

Fractional anisotropy

nfPPA patients showed an isolated reduction in FA within IFOF and UF territories in the left external capsule deep to the insula and ventrolateral prefrontal cortex (VL-PFC), extending to the superior temporal white matter (Fig. 2, top panel).

Axial diffusivity

Bilateral forceps minor, body, and genu of the CC and extensive portions of the prefrontal white matter including portions of the anterior SLF territory showed increased D_A in nfPPA patients. Portions of the anterior limb of the IC/ATP also showed this pattern. In the right hemisphere, dorsal involvement stretched along the corona radiata into the parietotemporal white matter and forceps major. Ventral tracts showed involvement of anterior IFOF and UF territories. Left hemisphere superior and middle temporal white matter was also affected, including portions contributing to the ILF (Fig. 2, top panel).

Radial diffusivity

D_R increases were widespread. In anterior regions, they occurred in similar areas to D_A increases, including forceps minor and prefrontal white matter as well as ventral tracts. Dorsally, D_R increases extended to the posterior extent of the corona radiata, with substantially greater bilateral spread than D_A (Fig. 2, bottom panel).

Voxel-based morphometry

Patients with nfPPA showed significant atrophy largely in left hemisphere sites. There was distributed atrophy of the left prefrontal region, including the medial frontal, frontal polar, middle and superior frontal gyri, and lateral inferior frontal regions, as well as small areas of the insula. Middle and superior temporal gyri were also involved, spreading from anterior regions to the temporoparietal region and small regions of the right superior temporal gyrus. Subcortical structures showed significant atrophy, including bilateral thalami and putamen, and the left caudate head. (Fig. 2).

Correspondence of VBM and DTI changes

Left hemisphere D_A and D_R changes occurred proximal to sites of subcortical atrophy in the anterior IC/ATP, and prefrontal white matter changes were proximal to atrophy in the inferior, middle, and superior frontal regions. However, frontal atrophy was largely limited to the left hemisphere, while D_A and D_R increases were widespread and bilateral.

DISCUSSION

This is the first DTI study to our knowledge that examines whole-brain white matter abnormalities in different PPA subtypes. We specifically accounted for total GM volume to examine those white matter changes that were not simply explained by global atrophy and found highly significant white matter abnormalities in both variants.

Figure 2.

DTI and VBM results from comparison of nine nfPPA patients to 16 controls. Areas of significant atrophy are shown in blue. Top row shows significant reductions in FA in patients in gold. Second row shows significant increases in D_A among patients in green, and third row shows significant increases in D_R among patients in red. Areas distant from atrophy are highlighted (white arrows). All images thresholded at $P < 0.05$, FWE corrected. Abbreviations as in text. Left side of coronal and axial brain images is right hemisphere.

svPPA patients showed disrupted white matter structure in ventral tracts projecting into the anterior temporal lobes, commensurate with the severe atrophy affecting this region. These changes were seen bilaterally in all three metrics, albeit less extensively in the right. These findings are in general agreement with past results (Borroni et al., 2007; Agosta et al., 2010; Whitwell et al., 2010; Galantucci et al., in press; Acosta-Cabronero et al., 2011). FA and D_R results revealed involvement of dorsal regions contributing to multiple portions of the SLF, with FA showing bilateral involvement. Past work has also found evidence for involvement of the left SLF in svPPA (Borroni et al., 2007; Whitwell et al., 2010), although some have argued its superior aspect is relatively spared in this syndrome

(Agosta et al., 2010; Whitwell et al., 2010; Galantucci et al., in press). Our TBSS results suggest for the first time that there is bilateral involvement of these SLF territories in svPPA. This likely reflects the disruption of arcuate fasciculus (AF) fibers running with the SLF II subcomponent (Makris et al., 2005; Agosta et al., 2010; Galantucci et al., in press), but there was also involvement in more medial and dorsal territories of the left hemisphere which could reflect disruption of the superior SLF I subcomponent (see white arrows on coronal section of Fig. 1 for FA and D_R) (Makris et al., 2005). Our finding of bilateral white matter involvement, including not only anterior temporal tracts but also commissural tracts of the CC, is consistent with the idea that semantic impairment involves disruption of bilateral

temporal lobe territories and disrupted connectivity between these regions (Visser et al., 2009; Warren et al., 2009; Lambon Ralph et al., 2010). While involvement of an anterior fusiform “hub” is most closely associated with the clinical svPPA syndrome (Mion et al., 2010), a recent meta-analysis of functional imaging studies found evidence for a semantic system involving prefrontal and parietal association cortices, as well as contributions from temporal cortex (Binder et al., 2009). Our findings suggest incipient involvement of a number of major tracts connecting multiple cortical regions in svPPA, including ventral tracts and the AF likely projecting toward this hub region, but also other subcomponents of the SLF and commissural tracts.

It is also vital to compare these results to the recent study of Acosta-Cabronero et al. (2011), who used similar TBSS methods to examine a sample of svPPA patients. Our results are broadly consistent in that both studies show extensive bilateral involvement of ventral tract territories, and found that D_R was the most sensitive metric for detection of white matter abnormalities. Unique to our study is the bilateral involvement of more dorsal tract territories extending beyond the ventral temporal lobes, demonstrated in both FA and D_R results. While both studies made use of similar whole-brain TBSS analyses, it is likely that differences in patient severity are responsible for the present additional findings. Our sample had an appreciably lower mean MMSE score than those of Acosta-Cabronero et al. (2011) and more GM involvement beyond the anterior temporal regions. In light of this, it is possible that our sample represents a more severe stage of disease, though duration was not reported in their study. This is in keeping with a model of semantic system disruption that progresses along with the clinical decline of svPPA. White matter regions of key tracts in this system beyond the anterior temporal region may become gradually more involved, notably including bilateral involvement of more distant portions of the horizontal AF and possibly more dorsal SLF territories. Indeed, Acosta-Cabronero et al. (2011) noted that at a lenient statistical threshold, the D_R changes found in the anterior temporal lobe spread into the AF within the parietotemporal white matter. In this sense, our study provides a complementary snapshot of svPPA, likely further down the degenerative pathway. Of course, the small patient groups in each study warrants a cautionary note, and we await longitudinal data in larger samples to confirm this pattern of white matter disruption in svPPA.

In contrast to svPPA, FA proved to be a relatively insensitive marker of white matter disruption in nfPPA patients when GM atrophy was accounted for, while diffusivity changes were markedly widespread. This finding emphasizes the importance of examining multiple DTI metrics to elucidate a complete, if complex, picture of white matter disruption (Acosta-Cabronero et al., 2010). D_A showed bilateral increases of ventral and dorsal frontal white matter in addition to the forceps minor, similar to past findings in a sample of FTD patients (Zhang et al., 2009).

However, these changes also spread along the frontoparietal white matter, particularly in the right hemisphere. D_R increases were most striking and widespread, involving bilateral ventral and dorsal tracts, and again extensive involvement of the prefrontal white matter. These widespread diffusivity increases may explain the lack of sensitivity of FA in this group of patients. nfPPA was associated with widespread increases in both D_A and D_R , which would tend to balance each other and maintain the shape of the ellipsoid, leaving FA relatively unchanged. The focal FA changes deep to the insula and VL-PFC may represent a more severe stage of white matter disruption or a unique pathological process which could result in a different pattern of diffusivity changes. It is interesting to note that despite these white matter changes, atrophy of the anterior insula was minor. This is in contrast to past suggestions of insular atrophy as a hallmark of nfPPA (Gorno-Tempini et al., 2004; Grossman, 2010), but is in agreement with other studies in this subtype (Nestor et al., 2003; Wilson et al., 2010). It is possible that white matter changes contribute to the loss of function and connectivity of the insula and VL-PFC (Wilson et al., 2010), which may outstrip or precede the frank loss of neurons. Indeed, Nestor et al. (2003) found that while metabolism was significantly reduced in a sample of patients with nfPPA, GM atrophy was minor.

In comparing the pattern of diffusion findings between svPPA and nfPPA groups, there are clear differences in the relative sensitivity of different metrics (Fig. 3). Looked at in isolation, FA changes would suggest that svPPA is associated with widespread bilateral white matter involvement that extends beyond local areas of atrophy, while nfPPA show minimal focused changes. Diffusivity findings showed that increased D_R was the most widespread abnormality in both subtypes. However, nfPPA patients additionally showed widespread increases in D_A , while svPPA patients had D_A increases limited to ventral tracts. Indeed, the spread of both increased D_R and D_A was more pronounced in nfPPA patients than in those with svPPA. This suggests that nfPPA patients show a striking burden of white matter abnormalities represented largely by changes in the size of the diffusion ellipsoid (increased D_R and D_A) rather than its shape (FA), and these increases extend far beyond areas of GM loss. svPPA patients show this pattern less extensively, while alterations in the shape of the ellipsoid (reduced FA) are more pronounced. These contrasting patterns suggest that not only are different tract regions affected in these subtypes, but also that different pathological processes may be affecting white matter architecture in svPPA and nfPPA. This difference may reflect histopathological features associated with these clinical variants. While there is significant heterogeneity across cases, nfPPA is associated with tau-positive pathology including corticobasal degeneration (CBD) (Josephs et al., 2006), as well as a specific subtype of TDP-43 (type 3) (Sampathu et al., 2006; Josephs et al., 2009). Both of these are associated with direct involvement of white matter by

Figure 3.

Semitransparent overlay of atrophy and diffusion findings. Grey matter atrophy in blue. Skeleton regions showing reduced FA in yellow, increased D_R in red, and increased D_A in green. Areas of proximal overlap of FA change and atrophy show as grey. D_R and atrophy show as purple. Areas of proximal overlap of D_A

and atrophy show as turquoise. Both groups show most widespread changes in D_R . nfPPA patients show focal FA reductions, but widespread D_R and D_A increases, spreading beyond sites of atrophy. svPPA patients show most widespread FA reductions and D_R increase, but limited D_A increase.

pathological inclusions: CBD is associated with astrocytic tangles and coiled bodies in oligodendrocytes (Cairns et al., 2007), and white matter in the frontal lobe may be directly affected by these tau-positive inclusions (Sanchez-Valle et al., 2006; Tokumaru et al., 2009). TDP-43 type 3 is likewise associated with white matter inclusions in oligodendrocytes of temporal and frontal lobes (Neumann et al., 2007). In contrast, svPPA may be less pathologically heterogeneous. svPPA is closely associated with TDP-43 type 1 (Davies et al., 2005; Josephs et al., 2009; Rohrer et al., 2010b), which shows less evidence of direct white matter involvement (Neumann et al., 2007). This dissociation may lead to different patterns of white matter disruption, which could ultimately be reflected in the diffusion patterns seen here. It is possible that nfPPA is associated with a larger burden of direct white matter pathology, which may be associated with widespread changes in both D_R and D_A , compared to svPPA patients. While increases in D_R and reductions in D_A have been attributed to loss of myelin or axonal damage, respectively (Song et al., 2002), this relationship may not hold in diseased tissue (Wheeler-Kingshott and Cercignani, 2009), and there is currently no clear understanding of what increases in both D_R and D_A represents pathologically. As such, we refrain from specu-

lating on the specific nature of white matter damage that may be responsible for these patterns. In any case, these findings suggest that future investigation of the relationship between diffusivity measures and underlying histopathology could be fruitful. A very recent study by Galantucci et al. (in press) also found differences in diffusivity metrics across PPA subtypes, and likewise suggest that these may be related to the underlying nature of white matter pathology. Their findings differed markedly from ours in that they found no D_A differences in their nonfluent patients. This may be explained partially by methodological differences, as their tractographic analysis focused on specific association tracts of interest, which likely did not capture the extent of prefrontal and callosal white matter involvement found here. Tractographic analyses also average values over voxels within a tract region, which could wash out discrete areas of difference that may be picked up with a voxelwise technique that focuses on comparing peak values, such as TBSS. It is notable that they reported mean D_A values that were higher among nfPPA patients than controls in all but one tract region, but these did not reach significance. Despite these differences, there is growing evidence that DTI measures may be useful for interrogating the underlying pathological

process in different neurodegenerative conditions. Indeed, the organized nature of white matter tissue offers unique advantages for this purpose over imaging studies focused solely on relatively unstructured GM.

Finally, the finding that these white matter changes were not accounted for by global GM atrophy warrants a point of discussion. This finding confirms that DTI provides unique additional information in the setting of PPA that is not simply accounted for by global changes in GM volume (cf., Bosch et al., 2010). However, this does not argue for a complete divorce of WM and GM pathology in PPA. Indeed, while there is evidence noted above that some subtypes of PPA may show direct WM pathological lesions (Neumann et al., 2007), it is likely that the bulk of WM pathology is as a result of axonal degeneration following from pathological changes to cell bodies in the affected GM regions (Acosta-Cabronero et al., 2011). Our findings simply confirm that DTI provides a unique, sensitive imaging measure in these syndromes, and reveals highly salient differences that do not covary directly with the global degree of GM loss measured on conventional structural imaging. Indeed, DTI measures may be a more sensitive measure of pathological change than structural volumetry, most persuasively demonstrated here by the extensive bilateral increases in directional diffusivities in *nfPPA* patients, who showed limited left-hemisphere changes in GM density. See Supporting Information for a discussion of the GM covariate.

There are several limitations to consider in this study. TBSS and VBM require non-linear registration of images, which can introduce uncertainties if this registration is sub-optimal. While this issue cannot be completely eliminated, TBSS offers certain advantages over other voxelwise techniques (Borroni et al., 2007) via the projection of local maxima onto the skeleton to account for residual misregistration, and avoiding issues around the impact of spatial smoothing (Jones et al., 2005; Smith et al., 2006). TBSS allows a whole-brain assessment of affected white matter areas but is limited in the inferences that can be made about which specific tracts are affected. While this is a drawback of our chosen technique, these results provide a complementary viewpoint to the existing literature, which has largely used region of interest and tractography methods to examine specific tracts (Agosta et al., 2010; Whitwell et al., 2010; Galantucci et al., in press). TBSS allows us to examine the entire body of white matter and relate it topographically to GM changes, without restriction to a set of tracts in a particular hemisphere (Agosta et al., 2010) or hand-placed ROIs (Whitwell et al., 2010). Our acquisition protocol includes 23 separate gradient directions, which may be below the optimal level for calculation of diffusivity measurements, though FA is likely to be stable above 20 directions (Jones, 2004). While this may have added variance to measures of diffusivity and reduced sensitivity for detecting all possible group differences, it should be noted that we collected two repetitions to reduce the impact of noise. A final limitation, shared by studies of rare syndromes, is our small sample

size. While similar in size to past work, comparisons with the existing literature should consider the modest sample sizes and heterogeneity of patients across the literature. In our sample, symptom duration showed a trend toward being longer among the *svPPA* patients, suggesting they may be at a more advanced stage of their disease. Although this remains a possibility, the groups were well matched on general measures of cognitive status and dementia severity (MMSE, MoCA, and DRS), and aphasia severity (aphasia quotient of the Western Aphasia Battery). Ultimately, larger samples of patients at different disease stages will be needed to firmly establish patterns in rare syndromes such as PPA.

CONCLUSIONS

Taken together, these results highlight the important and distinct contribution of white matter disruption to *svPPA* and *nfPPA*. It is important to note that while there were clear differences in the regions affected in these subtypes, there was no absolute territorial dissociation in the affected tract territories. Both *svPPA* and *nfPPA* showed involvement of dorsal and ventral tracts. The notable differences between these variants in the relative sensitivity of FA and diffusivity measures may have implications for the histopathological underpinnings of these two neurodegenerative conditions.

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