Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia

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ABSTRACT

Objective: To use diffusion tensor imaging (DTI) to assess gray matter and white matter tract diffusion in behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SMD), and progressive nonfluent aphasia (PNFA).

Methods: This was a case-control study where 16 subjects with bvFTD, 7 with PNFA, and 4 with SMD were identified and matched by age and gender to 19 controls. All subjects had 3-T head MRI with a DTI sequence with diffusion encoding in 21 directions. Gray matter mean diffusivity (MD) was assessed using a region-of-interest (ROI) and voxel-level approach, and voxel-based morphometry was used to assess patterns of gray matter loss. White matter tract diffusivity (fractional anisotropy and radial diffusivity) was assessed by placing ROIs on tracts of interest.

Results: In bvFTD, increased gray matter MD and gray matter loss were identified bilaterally throughout frontal and temporal lobes, with abnormal diffusivity observed in white matter tracts that connect to these regions. In SMD, gray matter loss and increased MD were identified predominantly in the left temporal lobe, with tract abnormalities observed in the inferior longitudinal fasciculus and uncinate fasciculus. In PNFA, gray matter loss and increased MD were observed in left inferior frontal lobe, insula, and supplemental motor area, with tract abnormalities observed in the superior longitudinal fasciculus.

Conclusions: The diffusivity of gray matter is increased in regions that are atrophic in frontotemporal dementia, suggesting disruption of the cytoarchitecture of remaining tissue. Furthermore, damage was identified in white matter tracts that interconnect these regions, supporting the hypothesis that these diseases involve different and specific brain networks. *Neurology*® 2010;74:1279-1287

GLOSSARY

AAL = automated anatomic labeling; **AC** = anterior cingulate; **ADRC** = Alzheimer's Disease Research Center; **ADPR** = Alzheimer's Disease Patient Registry; **AOS** = apraxia of speech; **bvFTD** = behavioral variant frontotemporal dementia; **CV** = coefficient of variation; **DA** = axial diffusivity; **DR** = radial diffusivity; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FDR** = false discovery rate; **FOV** = field of view; **FTD** = frontotemporal dementia; **FWHM** = full-width at half-maximum; **GCC** = genu of the corpus callosum; **HDW** = high-dimensional warping; **ILF** = inferior longitudinal fasciculus; **MD** = mean diffusivity; **MPRAGE** = magnetization prepared rapid acquisition gradient echo; **PC** = posterior cingulate; **PNFA** = progressive nonfluent aphasia; **PVC** = partial volume correction; **ROI** = region of interest; **SLF** = superior longitudinal fasciculus; **SMD** = semantic dementia; **UNC** = uncinate fasciculus.

Diffusion tensor imaging (DTI) has recently emerged as a valuable technique for assessing structural changes in the brain.¹⁻³ It can provide information on microstructural tissue integrity by measuring changes in water diffusion through tissue. This is particularly useful for assessing the integrity of white matter tracts because DTI can provide a measure of the directionality of diffusion (fractional anisotropy [FA]). However, DTI can also provide a measure of the magnitude of diffusivity (mean diffusivity), which is typically increased in neurodegeneration because of loss of microstructural barriers to diffusion, and can be used to assess the integrity of gray matter.

The frontotemporal dementias (FTDs) are a group of neurodegenerative disorders that are associated with unique and focal patterns of gray matter atrophy.⁴⁻⁷ These disorders include

Supplemental data at
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From the Departments of Radiology (J.L.W., R.A., K.K., A.S., H.A.E., P.V., C.R.J.), Information Technology (M.L.S.), Biostatistics (S.D.W.), and Neurology (Behavioral Neurology) (D.S.K., B.F.B., R.C.P., K.A.J.), Mayo Clinic Rochester, MN.

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behavioral variant FTD (bvFTD), which is characterized by behavior and personality changes; progressive nonfluent aphasia (PNFA), characterized by phenomic errors and hesitant speech; and semantic dementia (SMD), characterized by naming problems.⁸ There is some evidence that bvFTD and SMD are associated with white matter tract degeneration,⁹⁻¹³ although DTI has not previously been assessed in PNFA, and it is unclear how patterns of tract degeneration differ across these variants.

The aim of this study was therefore to assess water diffusivity in white matter tracts and gray matter, and to compare these results with the patterns of gray matter atrophy in bvFTD, SD, and PNFA. We hypothesize that patterns of abnormal gray matter diffusivity will overlap with patterns of atrophy, although this is currently unknown.

METHODS Subjects. We identified all subjects (n = 27) from the Mayo Clinic Rochester Alzheimer's Disease Research Center (ADRC) or Patient Registry (ADPR) who fulfilled clinical criteria for FTD (16 bvFTD, 7 PNFA, 4 SMD),⁸ were recruited between July 2007 and October 2008, and had DTI-MRI. These subjects were frequency-matched by age and gender to 19 normal controls who had been recruited into the ADRC or ADPR. Subject demographics are shown in table 1.

Standard protocol approvals and consent. Informed consent was obtained for participation in the studies, which were approved by the Mayo Institutional Review Board.

Image acquisition. A standardized protocol was performed on a 3-T GE scanner (GE Healthcare, Milwaukee, WI). The DTI acquisition consisted of a single-shot echo-planar fluid-

attenuated inversion recovery pulse sequence used to suppress CSF signal. Imaging was performed in axial plane, with repetition time/inversion time 8,800/2,200 milliseconds, in-plane matrix 128/122 (reconstructed 128 × 128), field of view (FOV) 38 cm, phase FOV 0.62, 21 diffusion encoding steps, in-plane resolution 3 mm, and slice thickness 3.3 mm. Parallel imaging with a SENSE factor of 2 was used. The protocol also included a 3-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence as previously described.¹⁴

Voxel-based morphometry. Patterns of gray matter atrophy were assessed using voxel-based morphometry¹⁵ in SPM5. Scans were normalized to the Montreal Neurological Institute template, segmented using unified segmentation and averaged to create customized templates and prior probability maps. All images were then normalized to the customized template and segmented using the customized tissue probability maps into gray matter, white matter, and CSF,¹⁶ followed by the hidden Markov random field cleanup step.¹⁷ Gray matter images were modulated and smoothed at 8-mm full-width at half-maximum (FWHM).

DTI processing. Each of the 21 diffusion-weighted images was registered to the nondiffusion weighted b0 volumes using 12-df affine registration. Maps of FA, color-coded FA, mean diffusivity (MD), axial diffusivity (DA) (equivalent to eigenvector 1), and radial diffusivity (DR) (average of eigenvectors 2 and 3) were computed from these 21 diffusion-weighted images using DtiStudio.¹⁸ To maintain a clear distinction between cortex and tract measurements, MD was assessed in gray matter regions that lack directional diffusion, with FA, DR, and DA assessed in white matter tracts since the diffusion is inherently directional.

Gray matter diffusivity measurements. Gray matter diffusivity was measured using both an atlas-based parcellation and voxel-level analysis. The atlas-based parcellation technique used the automated anatomic labeling (AAL) atlas¹⁹ and SPM5 to generate mean MD values for different regions of interest (ROIs). We analyzed 16 mutually exclusive ROIs covering left and right frontal, temporal, parietal, and occipital lobes and basal ganglia.

The AAL atlas¹⁹ was normalized to a customized template¹⁶ and edited. Each MPRAGE was normalized to the customized template, and the inverse transformation was applied to warp the atlas labels to the subject's native anatomical space (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). Each MPRAGE was segmented into gray matter, white matter, and CSF in native space. Next, the MPRAGE of each subject was warped to the b0 image using an in-house modified version of the high-dimensional warping (HDW) toolbox in SPM5. The resulting deformation was applied to the subject-specific atlas, as well as to the segmented images. For each subject, the b0-space segmented gray and white matter segmentations were combined to create a binary brain mask. Each subject's brain mask was multiplied by the subject-specific b0-space atlas, to generate a custom atlas for each subject, parcellated into the aforementioned ROIs. The b0-space gray and white matter images were used to perform partial volume correction (PVC) on the MD image, using a 2-compartment PVC algorithm.²⁰ PVC-corrected MD values were calculated for all gray matter ROIs in the atlas.

For the voxel-level analysis, each PVC-corrected MD image was transformed into template space by inverting the deformation obtained for the HDW of each MPRAGE to b0 space, combined with the transformation performed above to normal-

Table 1 Subject demographics^a

	Controls (n = 19)	bvFTD (n = 16)	SMD (n = 4)	PNFA (n = 7)	p Value
No. of women (%)	13 (68)	7 (44)	2 (50)	4 (57)	0.52 ^b
Age, mean (SD), y	65.3 (4.8)	59.1 (11.0)	67.0 (7.0)	63.9 (7.4)	0.11 ^c
Education, mean (SD), y	15.4 (2.6)	14.6 (2.5)	15.0 (3.8)	14.3 (2.3)	0.76 ^c
MMSE score, mean (SD)	29.3 (0.9)	21.1 (5.5)	15.7 (11.0)	21.8 (7.3)	0.40 ^d
CDR sum of boxes, mean (SD)	0.0 (0.1)	7.8 (5.1)	8.3 (6.8)	4.5 (5.2)	0.37 ^d
Time from dementia onset to scan, mean (SD), y	—	8.4 (7.5)	6.8 (2.9)	5.5 (4.2)	0.60 ^d

Abbreviations: bvFTD = behavioral variant frontotemporal dementia; CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; PNFA = progressive nonfluent aphasia; SMD = semantic dementia.

^aMMSE missing for 2 patients with bvFTD, 1 with SMD, and 1 with PNFA. Four controls had the MMSE estimated based on the Short Test of Mental Status. One patient with PNFA did not report level of education.

^bFisher exact test performed among all 4 groups.

^cAnalysis of variance among all 4 groups.

^dAnalysis of variance among the 3 frontotemporal dementia variants.

Figure 1 Illustration of placement of fractional anisotropy regions of interest

Fractional anisotropy color map from a control subject illustrating the placement of the white matter tract regions of interest. Regions of interest have been placed in the left hemisphere only. AC = anterior cingulate; ant = anterior; CST = corticospinal tract; GCC = genu of the corpus callosum; ILF = inferior longitudinal fasciculus; PC = posterior cingulate; post = posterior; SCC = splenium of the corpus callosum; SLF = superior longitudinal fasciculus; sup = superior; UNC = uncinate fasciculus.

ize each MPAGE into template space. An 8-mm FWHM smoothing filter was applied.

White matter tract diffusivity measurements. Specific white matter tracts were identified using the color-coded FA maps. ROIs were placed on the tracts on the color-coded FA maps using ANALYZE software (Mayo Biomedical Imaging Resource, Rochester, MN) by 1 rater (J.L.W.) blinded to clinical diagnosis. Regions were placed using anatomic landmarks on axial images, but coronal images were viewed simultaneously to guide placement. ROIs were placed on the following tracts (figure 1): genu of the corpus callosum (GCC), splenium of the corpus callosum, uncinate fasciculus (UNC) at the vertical position where it connects temporal and frontal lobes, inferior longitudinal fasciculus (ILF), anterior cingulate (AC), posterior

cingulate (PC), superior longitudinal fasciculus (SLF), and the descending corticospinal/corticopontine tracts. The SLF was sampled at 3 positions: anterior descending tracts branching into the inferior frontal lobes, posterior descending tracts branching into posterior temporal lobes, and superior horizontal fibers usually positioned adjacent to the most superior slice of the lateral ventricles. The ILF was sampled at an anterior and posterior position within the temporal lobe. All ROIs were measured separately for the left and right hemispheres, except for the corpus callosum. Once the ROIs had been placed using color-coded FA maps, they were overlaid on FA, DA, and DR maps to calculate tract statistics for each ROI.

Intrarater reproducibility was assessed by placing ROIs on 20 subjects twice with an interval of 2 weeks. The rater was blinded to ROI placement at time 1 when placing ROIs at time 2.

Statistics. To assess reproducibility, we estimated within-subject coefficient of variation (CV) for each ROI by fitting an intercept-only mixed effects model with a random patient effect and, when applicable, a random side-within-patient effect.²¹ Left and right ROIs from the same subject were treated as separate, albeit correlated, observations.

To assess the gray matter and white matter tract ROI data, we fitted analysis of covariance models with 4-level group effects for each ROI within each endpoint (FA, DA, DR, and gray matter MD) with age and gender included as covariates. We estimated pairwise differences with 95% confidence intervals and performed pairwise hypothesis tests using contrasts from the model. To control the number of false-positive pairwise differences, we applied a false discovery rate (FDR) correction,²² which controls the proportion of false-positives across the p values for all ROIs for each endpoint. Significance was considered at $p < 0.05$ and at trend level to $p < 0.1$. If comparisons did not survive correction using FDR, uncorrected p values at $p < 0.05$ were reported.

To assess gray matter volume and MD at the voxel level, we applied full-factorial models in SPM5 to assess differences between disease groups and controls with age and gender included as covariates. The MD analysis was masked by the gray matter template with a threshold of 0.05. The results for these voxel-level analyses were assessed uncorrected at $p < 0.001$.

RESULTS Gray matter voxel-level analyses. Patterns of gray matter volume loss and MD increase are shown in figure 2. The bvFTD group showed bilateral gray matter loss and MD increase throughout the frontal and anterior temporal lobes, with some involvement of the medial and lateral parietal lobes and occipital lobes. The SMD group showed loss and MD increase predominantly in the temporal lobes, particularly on the left, with loss extending into the occipital lobes. The PNFA group showed loss and MD increase in the left posterior inferior and superior frontal lobe, anterior insula, supplemental motor area, and temporal lobe.

Gray matter ROI diffusivity. The ROI-based gray matter results are shown in table e-1. The bvFTD group showed increases in MD across all ROIs, with the most significant increases bilaterally throughout the temporal and frontal lobes, insula, and caudate

Three-dimensional renderings of the brain showing the patterns of gray matter loss (left) and patterns of mean diffusivity (MD) increase (right) in behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SMD), and progressive nonfluent aphasia (PNFA) groups compared with controls. Results are shown uncorrected for multiple comparisons at $p < 0.001$.

nucleus. The most significant increases in MD in SMD were observed in left temporal lobe regions, with significant increases also observed in the right temporal lobe, insula, and left-sided frontal, parietal, and occipital lobes and caudate nucleus. No regions of increased MD survived the FDR correction in PNFA; however, there was a trend using uncorrected p values for increased MD in the bilateral inferior frontal lobes and the left supplemental motor area, insula, superior and medial frontal lobes, orbitofrontal cortex, temporal lobe, and precentral gyrus.

Significant differences across disease groups were only identified using uncorrected p values. bvFTD showed greater MD in the right temporal, medial frontal, precentral, and parietal lobes than PNFA; SMD showed greater MD in the left lateral temporal lobe than bvFTD and greater MD in the left temporal lobe, caudate, medial parietal and occipital lobe, and right medial temporal lobe than PNFA.

White matter tract ROI diffusivity. The mean of the within-subject CV^{21} estimates across all ROIs was 0.06 (range 0.03–0.10) for FA, 0.06 (0.02–0.13) for DR, and 0.05 (0.03–0.08) for DA.

White matter tract results are shown in table 2, figure 3, and figure e-2. In bvFTD, decreased FA and increased DR were identified in bilateral UNC, AC, anterior SLF, left posterior SLF, and anterior ILF,

with altered DR only in the GCC and posterior ILF. Increased FA was observed in the corticospinal tract. The SMD group showed significantly decreased FA and increased DR in the left posterior ILF, UNC, and PC. Increased DR was also found in the left anterior ILF, and decreased FA was found in the left anterior SLF. In contrast to the other groups, PNFA showed the most significant alterations in diffusivity in the SLF, with decreased FA and increased DR in the anterior SLF, and decreased FA in the left posterior and superior SLF and right UNC. No significant alterations in DA were identified in any tracts in any group.

Differences across the 3 disease groups were only identified using uncorrected p values; PNFA showed lower FA in the superior SLF than bvFTD, whereas bvFTD showed higher DR in the right anterior ILF than PNFA. SMD showed lower FA and higher DR in the left posterior ILF than both bvFTD and PNFA.

DISCUSSION This study has demonstrated that FTD is associated with changes in both gray matter and white matter water diffusivity, and that patterns of change differ across the 3 syndromic variants of FTD.

Early DTI studies assessing white matter tracts typically reported FA, although more recent studies

Table 2 Mean ± SD white matter tract fractional anisotropy and radial diffusivity by clinical group

Region	Fractional anisotropy				Radial diffusivity			
	Controls	bvFTD	SMD	PNFA	Controls	bvFTD	SMD	PNFA
GCC	0.76 ± 0.06	0.69 ± 0.13	0.75 ± 0.06	0.76 ± 0.03	390 ± 99	515 ± 219 ^a	403 ± 80	375 ± 49
SCC	0.84 ± 0.05	0.82 ± 0.06	0.83 ± 0.07	0.81 ± 0.05	278 ± 102	308 ± 122	271 ± 56	288 ± 43
AC								
L	0.51 ± 0.08	0.43 ± 0.11 ^b	0.41 ± 0.04	0.46 ± 0.09	544 ± 61	667 ± 128 ^b	618 ± 53	634 ± 83
R	0.45 ± 0.05	0.38 ± 0.06 ^b	0.41 ± 0.03	0.40 ± 0.08	584 ± 51	680 ± 77 ^b	631 ± 24	640 ± 67
PC								
L	0.55 ± 0.06	0.53 ± 0.09	0.46 ± 0.03 ^a	0.53 ± 0.07	471 ± 57	496 ± 70	561 ± 57 ^a	506 ± 59
R	0.56 ± 0.07	0.54 ± 0.09	0.50 ± 0.05	0.54 ± 0.09	462 ± 59	512 ± 86 ^a	513 ± 54	481 ± 45
UNC								
L	0.52 ± 0.07	0.43 ± 0.10 ^b	0.40 ± 0.09 ^a	0.45 ± 0.10	512 ± 74	666 ± 136 ^b	687 ± 102 ^b	613 ± 88
R	0.54 ± 0.08	0.42 ± 0.10 ^b	0.44 ± 0.10	0.43 ± 0.09 ^a	500 ± 77	661 ± 126 ^b	625 ± 103	574 ± 79
ILF anterior								
L	0.49 ± 0.08	0.46 ± 0.08	0.42 ± 0.06	0.43 ± 0.05	559 ± 78	652 ± 88 ^b	705 ± 85 ^b	651 ± 38
R	0.48 ± 0.09	0.41 ± 0.06 ^b	0.47 ± 0.05	0.45 ± 0.04	576 ± 79	701 ± 126 ^b	638 ± 29	595 ± 47
ILF posterior								
L	0.59 ± 0.07	0.55 ± 0.05	0.48 ± 0.05 ^b	0.58 ± 0.02	508 ± 82	575 ± 96 ^b	712 ± 118 ^b	520 ± 43
R	0.57 ± 0.07	0.55 ± 0.07	0.56 ± 0.03	0.55 ± 0.06	522 ± 89	571 ± 104 ^a	556 ± 41	538 ± 44
SLF anterior								
L	0.48 ± 0.06	0.41 ± 0.06 ^b	0.38 ± 0.05 ^a	0.41 ± 0.08 ^a	534 ± 62	582 ± 84 ^b	617 ± 43	605 ± 70
R	0.45 ± 0.04	0.40 ± 0.07 ^b	0.39 ± 0.02	0.35 ± 0.05 ^b	532 ± 52	590 ± 67 ^b	602 ± 45	639 ± 76 ^b
SLF posterior								
L	0.59 ± 0.07	0.51 ± 0.09 ^b	0.53 ± 0.04	0.50 ± 0.09 ^a	462 ± 76	569 ± 141 ^b	587 ± 106	553 ± 68
R	0.54 ± 0.08	0.52 ± 0.07	0.46 ± 0.10	0.51 ± 0.08	490 ± 81	533 ± 90	590 ± 76	518 ± 65
SLF superior								
L	0.60 ± 0.05	0.59 ± 0.06	0.53 ± 0.06	0.53 ± 0.07 ^a	437 ± 50	471 ± 71	514 ± 63	502 ± 65
R	0.58 ± 0.06	0.57 ± 0.07	0.58 ± 0.06	0.57 ± 0.05	447 ± 57	481 ± 93	461 ± 47	479 ± 80
CST								
L	0.54 ± 0.07	0.56 ± 0.07	0.61 ± 0.06	0.55 ± 0.05	485 ± 57	491 ± 70	465 ± 51	494 ± 54
R	0.51 ± 0.06	0.54 ± 0.07 ^b	0.55 ± 0.07	0.52 ± 0.03	493 ± 54	500 ± 78	471 ± 26	490 ± 49

Abbreviations: AC = anterior cingulate; bvFTD = behavioral variant frontotemporal dementia; CST = corticospinal tract; GCC = genu of the corpus callosum; ILF = inferior longitudinal fasciculus; PC = posterior cingulate; PNFA = progressive nonfluent aphasia; SCC = splenium of the corpus callosum; SLF = superior longitudinal fasciculus; SMD = semantic dementia; UNC = uncinate fasciculus.

^a $p < 0.10$, ^b $p < 0.05$ vs controls based on false discovery rate-corrected analysis of covariance p value.

have moved toward reporting DR and DA, where increases in DR have been interpreted as reflecting loss of myelin integrity²³ and increases in DA represent axonal degeneration. However, it was recently suggested that alignment of the eigenvectors with underlying tissue could be affected by disease pathology, and so this interpretation may not always hold.²⁴ This criticism of DR and DA does not extend to FA, which is still considered to represent a valid measure of the degree to which water diffusion is directional. Therefore, although we report DR and DA for consistency with previous studies, caution should be exercised in interpreting these data. Tract abnormal-

ities were observed in all disease groups, although changes were only identified in FA and DR.

bvFTD was associated with widespread patterns of increased gray matter MD, particularly affecting bilateral temporal and frontal lobes, but also the parietal lobes. These changes closely mirrored the patterns of gray matter loss in the same subjects, suggesting a close spatial association between atrophy and increases in water diffusion and showing that the remaining tissue has abnormalities that can be detected using DTI. Patterns of predominantly frontal and temporal gray matter loss are typical for bvFTD.^{7,25-27} We also identified diffusivity changes

Figure 3 Box plots showing the distribution of fractional anisotropy values for the disease groups

To aid comparison, fractional anisotropy (FA) values were centered at the region of interest (ROI)-specific control group mean (defined as zero on the horizontal axis) and thus can be interpreted as differences between each disease group and controls for each white matter tract ROI. The boxes indicate the 25th, 50th (median), and 75th percentiles of the distributions, whereas the horizontal lines extending from the boxes stop at the most extreme data points. AC = anterior cingulate; ant = anterior; bvFTD = behavioral variant frontotemporal dementia; CST = corticospinal tract; GCC = genu of the corpus callosum; ILF = inferior longitudinal fasciculus; PC = posterior cingulate; post = posterior; PNFA = progressive nonfluent aphasia; SCC = splenium of the corpus callosum; SLF = superior longitudinal fasciculus; SMD = semantic dementia; sup = superior; UNC = uncinate fasciculus. * $p < 0.10$, ** $p < 0.05$ vs controls based on false discovery rate-corrected analysis of covariance p value.

in many white matter tracts in bvFTD. These were typically tracts that connected the regions of atrophic brain tissue. Diffusivity changes were identified in tracts located in the frontal lobes, such as the AC, GCC, and anterior SLF, and tracts that connect to the temporal lobes, such as the UNC and ILF. The changes observed in the ILF were particularly severe in anterior portions of the tract, which corresponds to the fact that gray matter loss was most severe in the anterior temporal lobe. However, changes in diffusivity were also identified in more posterior ROIs, such as the posterior SLF, and in the PC. Although bvFTD is typically considered to involve the anterior temporal and frontal lobes, the lateral and medial parietal lobes can be severely affected²⁷ and usually become affected later in the disease course. It is also possible that our cohort consists of different anatom-

ical variants of bvFTD,²⁷ although we had too few subjects to allow further subdivision. A previous study similarly identified abnormal diffusivity in anterior corpus callosum, AC, and PC, and UNC in subjects with bvFTD, although they did not specifically identify and assess the ILF or SLF.¹³

The patterns of gray matter MD increase in SMD similarly matched well with the patterns of tissue loss. Both measures were associated with asymmetric patterns, with the most severe changes observed in the left hemisphere and particularly involving the temporal lobes. This pattern of atrophy is typical of subjects with SMD.^{6,7,28,29} Both gray matter loss and MD increases were also observed in the insula, frontal, parietal, and occipital lobes, with changes worse in the left hemisphere. Changes in white matter tract diffusivity were similarly identified in the left hemi-

sphere, with the most significant changes in FA and DR identified in the left anterior and posterior ILF and left UNC, which both connect to the temporal lobes. The ILF seems to be particularly related to SMD because it was involved to a greater degree than in bvFTD and PNFA. The ILF connects the temporal and occipital lobes³⁰ and has been suggested to play a role in visual object recognition and in linking object representations to their lexical labels.³¹ It is also likely that the ROI in the posterior ILF may contain fibers from the inferior fronto-occipital fasciculus, which has also been implicated in semantic processing,³² because these tracts overlap to a large degree. Although the UNC, which connects frontal and temporal lobes, has been suggested to be involved in semantic processing,³¹ the fact that it was also heavily involved in bvFTD supports the suggestion that it may not be essential for language³³ but may instead be contributing to behavioral dyscontrol,⁹ which can be present in both bvFTD and SMD. We also observed some changes in FA in the ROI placed in the left anterior SLF, which is positioned in the SLF as it descends into the inferior frontal lobe. This ROI may contain fibers from the arcuate fasciculus, which has previously been shown to have reduced FA in SMD⁹ and has been thought to play a role in language function.^{31,34,35}

Less severe gray matter changes were observed in PNFA. Increases in gray matter MD and gray matter loss were observed in left inferior and superior frontal lobe, insula, and supplemental motor area. Additional increases were observed in the left orbitofrontal cortex, medial frontal lobe, temporal pole, precentral gyrus, and right inferior frontal lobe. Previous studies have consistently found patterns of tissue loss in the inferior frontal lobes and insula in PNFA.^{5,29,36,37} The supplemental motor area has been shown to be associated with apraxia of speech (AOS),⁵ which is commonly found in patients with PNFA. Interestingly, the tract that showed the most severe changes in FA and DR was the SLF, with involvement of the anterior SLF tracts that descend into the inferior frontal lobes, the posterior SLF tracts that descend into the posterior temporal lobe, and the horizontal superior SLF tracts. In fact, PNFA was the only group to show significantly altered diffusivity in the superior SLF, and there was a trend for PNFA to show significantly lower FA in this tract compared with bvFTD. This result fits with the fact that the greatest regions of atrophy were identified in the inferior frontal lobes and suggests that damage to the SLF may play a role in the language deficits in PNFA. Abnormalities in the SLF have been previously reported in subjects with primary progressive aphasia.³⁴ However, the superior SLF ROI is also

likely to contain tracts that interconnect with motor and premotor regions.³⁵ It is therefore possible that damage to these tracts contributes to dysarthria and AOS that can be found in PNFA.⁵ The presence of AOS is associated with corticobasal degeneration pathology⁵ and previous studies of corticobasal syndrome have similarly reported diffusivity changes in the supplemental motor area and frontoparietal fibers, which likely coincide with the superior SLF.^{38,39} Detailed speech and language assessments were not available for the subjects in this study, however, and therefore the contribution of these motor problems is presently unclear.

This study has demonstrated differences in patterns of gray and white matter diffusion across the syndromic variants of FTD. Not all the results survived correction for multiple comparisons because of small numbers of subjects, but interesting trends were still identified. Damage to certain white matter tracts was relatively disease specific, with the AC and GCC only affected in bvFTD, the ILF preferentially affected in SMD, and the SLF being most heavily affected in PNFA. These abnormal tracts interconnect with the regions of abnormal gray matter in each disease, supporting the hypothesis that these diseases involve different large-scale neural networks.⁴⁰

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by Stephen D. Weigand, MS.

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CDC, AAN to Health Care Professionals: Monitor Patients for GBS

The Centers for Disease Control and Prevention (CDC) and the American Academy of Neurology (AAN) collaborated to reach out to neurologists across the US to monitor and report any possible new cases of Guillain-Barré syndrome (GBS) following 2009 H1N1 flu vaccination.

Neurologists and health care professionals nationwide who diagnose patients with vaccine-associated GBS should use the CDC and FDA Vaccine Adverse Event Reporting System (VAERS) to report their observations.

In addition, neurologists and all health practitioners in the 10 Emerging Infections Program (EIP) states—California, Connecticut, Maryland, Minnesota, New Mexico, New York, Colorado, Oregon, Georgia, and Tennessee—are asked to report all new cases of GBS, regardless of vaccination status, to their state's surveillance officer.

The AAN hosted a series of webinars providing an in-depth look at H1N1 vaccination and how it may pose a risk for GBS and information about the vaccination monitoring campaign.

For additional information about the monitoring campaign, or to watch the webinars or download VAERS form and information on reporting to surveillance officers in your state, visit the AAN's GBS toolkit page, www.aan.com/view/gbstoolkit.