A Diffusion Tensor Imaging Study of Cross-sectional and Longitudinal White Matter Alterations in Frontotemporal Lobar Degeneration

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Background: Behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA) are three major clinical subtypes of frontotemporal lobar degeneration (FTLD). While a few diffusion tensor imaging (DTI) studies have reported patterns of white matter degradation in bvFTD[1-3] and SD[4], little is known about the pattern of white matter alterations in PNFA. Furthermore, no longitudinal assessment of white matter changes in FTLD has been reported. In this study, we performed cross-sectional DTI using tractography-guided ROI as well as voxel-wise whole bran analysis of fractional anisotropy (FA), and diffusivities (DR, radial diffusivity; DA, axial diffusivity) to test the regional pattern of white matter alterations in these three distinct FTLD subtypes, compared to healthy controls (CN). Furthermore, we performed a preliminary longitudinal DTI analysis to examine white matter alterations in a small sample of FTLD with 1-year follow-up scans.

Methods: Twelve bvFTD patients (mean age=61.2±6.8yrs, mean MMSE=24.2±5.0), 6 SD patients (mean age=64.8±5.8yrs, mean MMSE=26.2±4.6), 6 PNFA patients (mean age=27.2±1.1yrs, mean MMSE=27.2±1.1) and 19 healthy controls (mean age=61.2±6.8yrs, mean MMSE=24.2±5.0) were included in the study. Four bvFTD, 3 SD and 2 PNFA patients had a second time scan after 1 year. DTI scans were performed on a 4 Tesla (Bruker /Siemens) MRI system, employing a spin-echo echo-planar sequence, with a factor 2 GRAPPA acceleration, TR/TE = 6000/77ms; 6 directions, b = 0, 800 s/mm^2, 2 x 2 mm^2 in-plane resolution; 40 continuous slices, each 3 mm thick; 4 averages. Using a tractography-guided ROI analysis[3], we measured mean FA (DR and DA) in the anterior/posterior corpus callosum (a.CC/p.CC), bilateral anterior/posterior cingulum (a.Cg/p.Cg), parahippocampus (pHP), uncinate fasciculus (Unc), arcuate fasciculus (AF) and fornix. Furthermore, we also performed voxel-wise analysis using SPM8 software by warping each FA image to a population-based FA template for spatial normalization and then smoothing the data with a 4mm^3 FWHM Gaussian kernel. Statistical differences between FTLD and CN groups were performed using a linear regression model with diagnosis as the main effect and age and gender as covariates. A longitudinal analysis assessing changes in the tracts was performed by first realigning the Time-2 FA images to the Time-1 FA image, using a linear registration. Fiber tracts generated from the Time-1 FA images served as ROIs and were placed on the Time-1 and Time-2 FA images to measure each Time points' mean FA. Statistical difference between Time-1 and Time-2 scans was tested using paired-samples T test.

Results: 1) Tract-guided analysis (Table 1): Compared to controls, bvFTD patients had significantly lower FA in the a.CC, left a.Cg, bilateral Unc, left AF and fornix fibers; SD patients had significantly lower FA in bilateral Unc, fornix and left pHP; whereas PNFA had lower FA only in the left AF and a.Cg fibers. 2) Regions with greater DR increases were similar to the regions with FA decreases, but fibers near the ventricles (e.g. CC, Fornix) had the greatest DR increases, these regions also had DA increases. 3) Whole brain analysis (Figure 1) showed a similar finding with that found from tract-guided analysis, that is, bvFTD had FA reduction in diffused white matter regions including the frontal and temporal brain; SD showed FA reduction in bilateral temporal white matter, particularly in the left Unc; and PNFA showed reduced FA in the left AF. 4) Longitudinal assessment showed that bvFTD had a significant FA reduction in a.CC over time (Table 2).

Conclusion: Consistent with previous reports, bvFTD is associated with a characteristic pattern of FA reductions in diffused frontal and temporal regions. SD affects temporal white matter, especially the left uncinate fasciculus that is involved in language. PNFA had white matter alterations in the left arcuate fasciculus, which is related to speech fluency. Preliminary longitudinal analysis suggests that DTI captures disease progression in FTLD.

Figure 1. Regional patterns of significantly reduced FA in FTLD subtypes (row-1: bvFTD; row-2: SD; row-3 PNFA) vs. CN. Statistical significance level was $P_{uncorrect}$=0.001

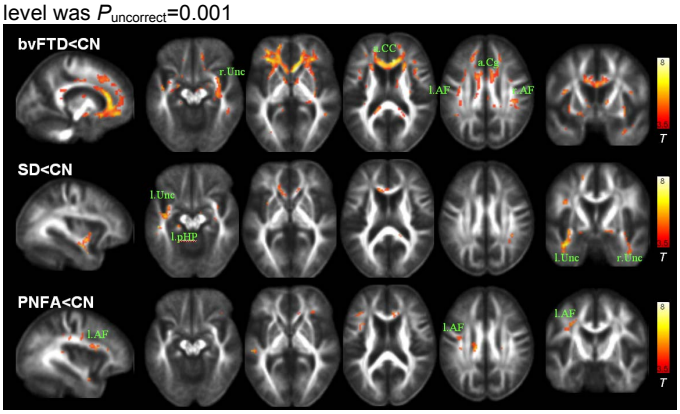

Table 1. Group comparisons of FA differences between FTLD subtypes and CN in specific fiber tracts

		bvFTD<CN *P*	SD <CN *P*	PNFA<CN *P*
a.CC		<0.001	n.s.	n.s.
p.CC		0.02	n.s.	—
a.Cg	**L.**	0.003	n.s.	0.03
	R.	n.s.	n.s.	n.s.
p.Cg	**L.**	n.s.	n.s.	n.s.
	R.	n.s.	n.s.	n.s.
pHP	**L.**	n.s.	0.02	n.s.
	R.	0.05	n.s.	n.s.
Unc.	**L.**	0.006	<0.001	n.s.
	R.	0.008	0.005	n.s.
AF	**L.**	0.02	n.s.	0.02
	R.	n.s.	n.s.	n.s.
Fornix		<0.001	<0.001	n.s.

Table 2. Annual change rates* of tract FA in FTLD subtypes

		bvFTD Mean (SD)	**SD** Mean (SD)	**PNFA** Mean (SD)
a.CC		**-7.5 (2.6)***	-2.8 (5.0)	-0.6 (0.7)
p.CC		-3.6 (3.0)	-1.4 (2.3)	4.1 (1.7)
a.Cg	**L.**	-5.3 (13.1)	0.8 (8.4)	-3.4 (2.4)
	R.	-6.5 (4.8)	4.5 (1.9)	-3.0 (7.1)
p.Cg	**L.**	-3.3 (10.3)	1.0 (1.6)	-0.4 (0.5)
	R.	-6.8 (3.9)	3.0 (4.2)	0.6 (6.3)
pHP	**L.**	-3.7 (8.7)	1.9 (0.7)	-2.1 (3.7)
	R.	-5.0 (6.5)	3.2 (5.2)	2.7 (10.7)
Unc.	**L.**	-3.4 (6.8)	-4.8 (1.1)	2.7 (1.6)
	R.	-4.4 (6.0)	-2.7 (3.2)	-2.0 (1.0)
AF	**L.**	-0.5 (6.8)	3.4 (7.6)	0.5 (0.9)
	R.	-2.9 (3.1)	0.3 (0.3)	-0.2 (1.4)
Fornix		1.1 (12.2)	-1.1 (3.1)	-1.2 (4.0)

Bold: Significant (P<0.05) reduction of FA at Time-2 *vs.* Time-1
* Annual change rate = (follow-up FA - baseline FA) / baseline FA / duration (mo) ×12 (mo)

Reference:
1. Borroni B, et al. Arch Neurol. 2007;64(2):246-51.. **2.** Matsuo K, et al. Neuroradiology. 2008;50(7):605-11. **3.** Y. Zhang, et al. Brain. 2009;132(Pt 9):2579-92. **4.** Agosta F, et al. in press. Brain. 2009