A diffusion tensor imaging study of longitudinal white matter degeneration in amyotrophic lateral sclerosis

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Background: Diffusion tensor imaging (DTI) studies have shown significant cross-sectional differences between patients with amyotrophic lateral sclerosis (ALS) and normal controls in the corticospinal tracts (CST)[1,2]. A few longitudinal studies[3,4] in ALS failed to find significant DTI alterations in regions of interest (ROI) of the CST in brain. The goal of this study was to investigate the longitudinal changes of DTI in bilateral CST using tractography-guided ROI analysis and voxel-wise whole brain analysis in ALS patients who were scanned at 7-month intervals.

Methods: Sixteen ALS patients (mean age 57.4 ± 10.3 yrs, 9 men, 7 women) were scanned at baseline (ALS-1) and after 7 months of follow-up (ALS-2). Twenty age- and sex-matched healthy subjects (mean age 57.5±9.2 yrs, 14 men, 6 women) were scanned only at baseline as controls (CN). Except two patients with co-morbid pathology, the remaining 14 ALS patients were further divided to two subgroups: 9 subjects with mild localized symptoms (ALS-L), and 5 subjects with severe generalized symptoms (ALS-G). DTI scans were performed on a 4 Tesla (Bruker /Siemens) MRI system with an 8-channel head coil, with TR/TE = 6000/77ms; 2 x 2mm^2 in-plan resolution, 40 continuous slices each 3 mm thick, b = 0, 800 s/mm^2, 6 directions, 4 averages, a GRAPPA factor of 2. For longitudinal analysis, the follow-up FA images were initially aligned to the baseline FA image using an affine registration method**.** Tractography-based analysis of the CST was performed on the baseline DTI images and the resulting fibers were used for ROI placement on the baseline and follow-up FA images, which were spatially aligned to the baseline FA images. Voxel-wise analysis was performed using SPM2 by spatially normalizing baseline and follow-up FA images to an FA template and smoothing with 4mm^3 FWHM Gaussian kernel. Finally, a general linear regression model was used with age and sex as covariates, to test differences between ALS and control groups, as well as the differences between ALS-L and ALS-G groups. A paired-samples T test was used to compare the difference between ALS-1 and ALS-2.

Results: 1) ALS *vs.* CN: both ALS-1 and ALS-2 had significantly decreased FA in the right CST (Table 1). Voxel-wise analysis revealed similar findings of FA decreases in the right CST and a few frontal regions (Figure 1, 1st row). 2) Longitudinal differences between ALS-2 and ALS-1: FA changed by -0.9% per year in the left CST, and -3.65% per year in the right CST. Paired sample T test showed that the right CSF had a significant (p=0.04) FA decline at follow-up compared to baseline, but the left CST did not (Table 1). Voxel-wise analysis revealed consistent findings with tract-guided analysis that the right motor fibers, middle corpus callosum which contains bilateral motor fibers, and some thalamic regions showed a significant FA reduction (Figure 1, 2nd row). 3) ALS-G *vs.* ALS-L: ALS-G group had significantly lower FA than the ALS-L group in CST, particularly on the left side. 4) Longitudinal differences in subgroups: ALS-L group had a significant decline (p=0.01) in FA over time, particularly on the right side, whereas the ALS-G group did not show significant changes over time (Table 2). Voxel-wise longitudinal analysis also revealed that the ALS-L group had a regional pattern of FA decline which was similar with the pattern that was seen in all ALS patients, whereas the ALS-G group did not. 5) The differences of MD were not significant in any of the tests.

Conclusion: These preliminary results suggest that longitudinal DTI measurements capture clinical progression of ALS. Furthermore, the difference in FA decline between generalized and localized ALS suggests different rates of disease progression across these two clinical ALS subgroups.

Table1. Changes of FA and MD values at baseline (ALS-1) and follow-up ALS (ALS-2).

		CN (n=20) Mean(SD)	ALS-1 (n=16) Mean(SD)	ALS-2 (n=16) Mean(SD)	Annual Change Rate (%)*	P ALS-2<ALS-1 (paired-T)
Left.CST	FA	0.533(0.02)	0.527(0.04)	0.524(0.05)	-0.90(7.7)	n.s.
	MD	0.857(0.03)	0.819(0.12)	0.802(0.09)	-1.44(20.2)	n.s.
Right.CST	FA	0.565(0.03)	**0.546(0.03)**	**0.534(0.03)**	-3.65(6.1)	0.04
	MD	0.789(0.04)	0.790(0.09)	0.797(0.09)	3.40(22.4)	n.s.

Bold: Differs from CN group at p≤0.05 (linear regression test)

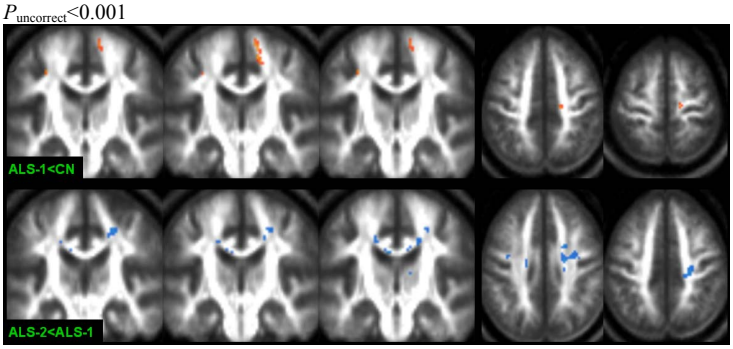
* Annual change rate = (follow-up FA- baseline FA) / baseline FA / duration (mo) × 12

Table2. Longitudinal changes of FA in groups of localized (ALS-L) and generalized (ALS-G) ALS subgroups.

	ALS subtypes	ALS-1 Mean(SD)	ALS-2 Mean(SD)	Annual Change Rate (%)*	*P* ALS-2<ALS-1 (paired-T)
Average.CST	ALS-L (n=9)	0.548(0.02)	0.541(0.02)	-2.44(2.1)	0.01
	ALS-G (n=5)	**0.505(0.02)**	**0.502(0.03)**	-1.41(7.3)	n.s.
Left.CST	ALS-L (n=9)	0.540(0.02)	0.538(0.02)	-0.25 (3.8)	n.s.
	ALS-G (n=5)	**0.485(0.03)**	**0.480(0.06)**	-2.46(13.4)	n.s.
Right.CST	ALS-L (n=9)	0.556(0.02)	0.543(0.02)	-4.5(5.2)	0.04
	ALS-G (n=5)	0.526(0.05)	0.524(0.05)	-0.81(4.1)	n.s.

Bold: FA in generalized ALS was significantly lower than in localized ALS at $P \leq 0.05$ (linear regression test).

Figure 1. 1st row: regions of significant FA reduction (warm color, by linear regression test) in the baseline ALS group (ALS-1) vs. Control group (CN). 2nd row: regions of significant FA reduction (cold color, by paired-samples t-test) in follow-up ALS group (ALS-2) vs. baseline (ALS-1). Significance level was $P_{uncorrect}<0.001$



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