



<b>Title</b>	<b>Asymptomatic members with SOD1 mutation in a large kindred with familial amyotrophic lateral sclerosis have abnormal water diffusion characteristics</b>
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# Asymptomatic members with SOD1 mutation in a large kindred with familial amyotrophic lateral sclerosis have abnormal water diffusion characteristics

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**Purpose/Introduction:** Amyotrophic lateral sclerosis (ALS) is a lethal disorder of unknown etiology, associated with progressive degeneration of motor neurons in corticobulbar (CBT) and corticospinal tracts (CST), resulting in muscle weakness, atrophy, bulbar and respiratory paralysis. At symptom-onset, more than 50% of motor neurons have degenerated. Fifty percent of patients die within 3 years, and 90% within 5 years from symptom-onset. No routine biomarkers or neuroimaging markers exist for ALS. The diagnosis is based clinically and on neurophysiology in symptomatic patients. Diffusion tensor imaging (DTI) detects the mobility of water molecules to yield structural order maps and directionality of white matter tracts. Previous DTI studies showed differences in diffusion pattern between ALS and controls. We explored DTI in a large multigenerational kindred with autosomal dominant ALS, with a known superoxide dismutase (SOD1) mutation. These familial cases (FALS) were indistinguishable clinically from sporadic patients (SALS). Some family members with the SOD1 mutation were asymptomatic (AFALS), possibly in a pre-symptomatic phase of ALS. In our study, we report the diffusion characteristics of FALS/SALS and AFALS using DTI. According to the best of our knowledge, we are the first group to carry out DTI study on subjects with AFALS.

**Subjects and Methods:** Cerebral DTI studies with 25 gradient directions (diffusion weighing=0 & 1000mm<sup>2</sup>s) were carried out at a 1.5T GE MRI System on 2 pairs of subject groups. Tables 1a and 1b show the details of the subject group pairs recruited. FALS/SALS was diagnosed using the revised El Escorial criteria. The DTI data were analyzed offline by two assessors who were blinded to the diagnosis. The diffusion toolbox<sup>1</sup> in SPM2 was used for the rigid-body registration and the reslicing of the intra-subject volumes with different gradient directions. DTI calculations were achieved using the standard Singular Value Decomposition (SVD) method in the DTIStudio<sup>2</sup>. Diffusion tensor Tractography (DTT) was performed by a blinded assessor in tracing the CBT/CST. Spatial normalization was then conducted on the fiber tracts, fractional anisotropy (FA) and tensor trace (TT) maps. Whole brain analysis and DTT-based analysis of the CBT/CST were both performed.

**Table 1a**

Subject group	Number	Age ±SD	Sex
FALS/SALS	7	49±18	6 males 1 female
Controls	11	49±15	7 males 4 females

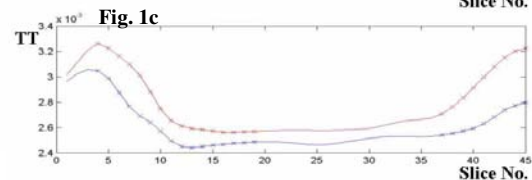
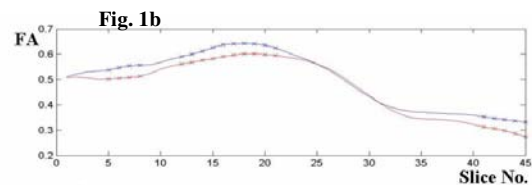
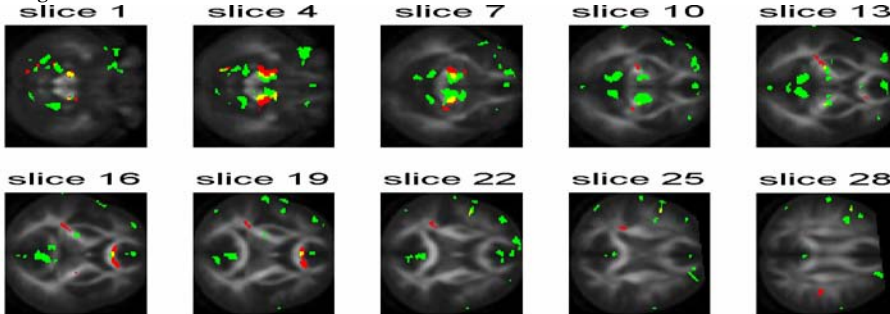
**Table 1b**

Subject group	Number	Age ±SD	Sex
AFALS	8	32±10	3 males and 5 females
Controls	13	31±9	5 males and 8 females

**Table 1b: subject groups**

**Results:** Figures 1 and 2 show comparisons between controls & FALS/SALS and between controls & AFALS respectively. The whole brain analysis was consistent with the DTT analysis in both cases. FA decrease and TT increase were found in the peduncle, internal capsule and sub-cortical white matter in FALS/SALS patients, which is consistent with the literature<sup>3</sup>. TT increase was also found in cerebellum and frontal lobe, which coincides with the previous report<sup>4</sup>. In AFALS, TT increase was found in cerebral peduncle, cerebellum and frontal lobe but to a much smaller extent compared with FALS/SALS.

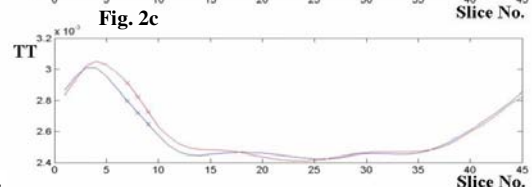
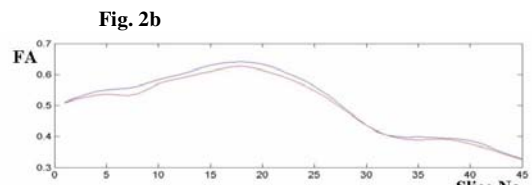
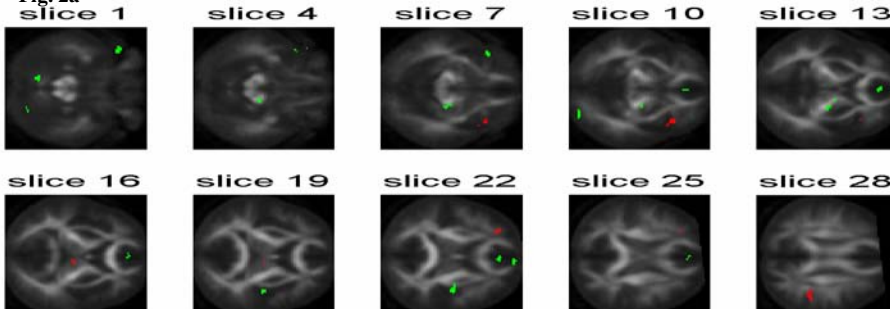
**Fig. 1a**



**Fig 1)** Comparison between FALS/SALS and controls. **(1a)** whole brain analysis (Red-FA decrease, green-TT increase, yellow-common,  $p < 0.005$ , extent threshold=25voxels). **(1b)** DTT analysis of FA of CBT/CST (red-FALS/SALS, blue-controls, cross-significant points with  $p < 0.04$  and extent threshold=6mm). **(1c)** DTT analysis of TT of CBT/CST (red-FALS/SALS, blue-controls, cross-significant points with  $p < 0.04$  and extent threshold=6mm).

**Fig 2)** Comparison between AFALS and controls.

**Fig. 2a**



**Discussion and Conclusions:** Our DTI studies showed significant difference in diffusion characteristics between FALS/SALS and healthy controls, consistent with previous reports. For AFALS, the TT value in regions similar to those found in ALS patients also had significant increase compared with controls. However, the extent was much smaller compared with FALS/SALS due to the fact that these subjects were in a pre-symptomatic phase of ALS. Our results suggested that diffusion changes may be detectable using DTI prior to symptom-onset. DTI may be useful as a neuroimaging marker for the diagnosis and progression of ALS.

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