Assessing white matter integrity with DTI in a large group of ALS patients

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Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative condition of complex pathology in humans, primarily involving motor neurons in the cerebral cortex (upper motor neurons, UMN), the brainstem and the spinal cord (lower motor neurons, LMN). It results in progressive weakness and wasting of the bulbar, limb, thoracic and abdominal musculature due to a loss of innervation of these muscles. Until now, the aetiology remains poorly understood and no curative therapies have been found. Both neurophysiologic and conventional neuroimaging techniques have been used to evaluate UMN pathology, but there are currently no sensitive techniques available in clinical practice for objectively assessing UMN damage at an early stage of the disease.

Earlier DTI studies (1,2) focussed on the brain stem and the lower parts of the CST only. These studies demonstrated reduction in fractional anisotropy (FA) and increase in mean diffusivity (MD) in regions of interest analyses of the CST.

The purposes of the present study are to evaluate changes in FA, MD, and fiber tracking parameters in the whole brain in a large group of ALS patients compared to sex and age matched controls, using fiber tracking and voxel-based analysis. We hypothesise that white matter changes in ALS are not limited to the CST but more diffuse.

Methods and materials

Thirty-three ALS patients and 21 controls were imaged on a 3T scanner (Intera, Philips, Best, the Netherlands) with a 8 channel phased array head coil. A DTI SE-EPI (matrix= 112x112; FOV= 220x220 mm; 68 saggital slices of 2.2 mm thickness; TR= 13781 ms; TE= 68 ms; 16 non-collinear directions with a *b*-value of 800 s/mm^2; gradient strength of 80 mT/m; SENSE reduction factor= 2; NSA= 2; TA = 8,52 minutes) and a T1-weighted coronal 3D TFE (182 contiguous coronal slices covering the whole brain and brainstem; FOV= 250x250 mm; TE= 4,6ms; TR= 9,7 ms; slice thickness= 1,2 mm; matrix= 256x256 mm; voxel size= 0,98x0,98x1,2 mm; TA = 6,3 minutes) were acquired.

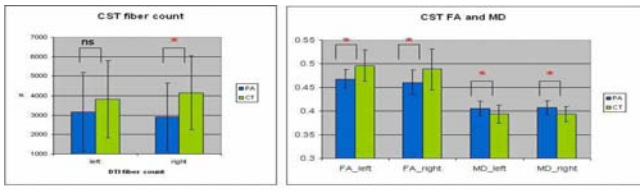
The DTI and 3D TFE data sets were transferred to a workstation (Pride, Philips, Best, the Netherlands). After a visual inspection of the DTI images for apparent artefacts, the DTI images were processed and coregistered to remove image distortion that arises from the effect of eddy currents on the EPI readout. Diffusion encoded FA maps were then calculated according to the scheme proposed by Pajevic and Pierpaoli (3). From these FA maps, DTI based color maps were generated. The reconstruction of the CST was performed by the Fiber Assignment by Continuous Tracking (FACT) method (4,5). The corticospinal tract was developed bilaterally both in patients and volunteers by tracking through two regions of interest (ROI) and an `AND´ operation using `brute force´ approach, by modification of the method described previously (6,7). The placement of ROIs (one in the precentral gyrus and one in the posterior limb of the internal capsule) was in accordance with anatomical knowledge and previous reports on the tracking of the CST (7). The experiment was blinded to avoid an observer-induced bias. Significant differences in FA, MD, and DTI fiber count were assessed using non-parametric Mann-Whitney-U tests.

The 3D TFE anatomical volumes were normalized to the MNI template using SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London). FA and MD maps were generated using FSL software (FMRIB Software Library, Release 3.2beta, 2004, The University of Oxford). In SPM2, these maps were further transformed so that the maps were brought in accordance with MNI space. FA and MD images were then smoothed with a 3D Gaussian kernel of FWHM 6mm. These images were entered in a voxel-based analysis (SPM2) using a two sample T-test.

Results

Fiber tracking of CST showed significant decrease of FA and significant increase of MD in ALS patients compared to healthy controls. A significant reduction in DTI fiber count was observed in the right CST, and a similar trend was present on the left side (Fig 1). When dividing the CST in motor and sensory part, the above mentioned changes were present in the motor part of the CST, whereas no significant changes of FA/MD were found in the sensory part.

In the voxel-based analysis, a distinct pattern of FA/MD changes was demonstrated, showing a significant increase of FA in ALS patients throughout the CST as well as in corpus callosum, frontal and parietal areas (Fig 2). A significant increase of MD in ALS patients was demonstrated in the caudal part of the CST.



p-value	MWU DTI_fiber_count_R	0,0267	MWU DTI_fiber_count_L	0,3609
	MWU FA_R	0,0012	MWU FA_L	0,0016
	MWU MD_R	0,0063	MWU MD_L	0,0267

Fig. 1: Mean FA/MD/DTI fiber count in ALS patients (PA, in green) and controls (CT, in blue), +/- standard deviation. * indicates significant changes

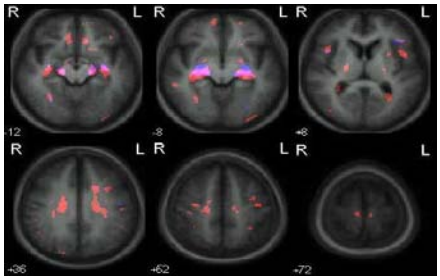


Fig. 2: Representative slices showing regions with significant decrease of FA (red) and significant increase of MD (blue) in the voxel-based analysis.

Conclusion

ALS patients indeed suffer from significant white matter loss mainly in the motor part of the corticospinal tract, in agreement with earlier studies (1,2). However, more diffuse changes are also present, notably a degeneration also occurs within the projection fibers from/to the primary motor cortex: corpus callosum, frontal and parietal areas.

References

(1) Ellis CM et al. Neurology 2001 Nov 13;57(9):1571-8.
(2) Toosy AT et al. Journal of Neurology Neurosurgery and Psychiatry 2003 Sep 1;74(9):1250-7.
(3) Pajevic S, Pierpaoli C. Magnetic Resonance in Medicine 1999 Sep;42(3):526-40.
(4) Pierpaoli C et al. Radiology 1996 Dec;201(3):637-48.
(5) Basser PJ, Pierpaoli C. Journal of Magnetic Resonance Series B 1996 Jun;111(3):209-19.
(6) Mori S et al. Ann Neurol 1999;45:265-9.
(7) Wakana S et al. Radiology 2004 Jan;230(1):77-87.