# Diffusion tensor imaging and proton MR spectroscopy in ALS

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## Introduction

Diffusion tensor imaging provides information about the axonal impairment in amyotrophic lateral sclerosis (ALS) by changes of the patterns of anisotropy, e.g. fractional anisotropy [1,2]. Proton MR spectroscopy is thought to assess biochemical markers for the neuronal and axonal integrity [3]. In this study, changes of FA in early ALS were investigated by a voxel based analysis without any a priori hypothesis, and changes of the FA in ALS in a subcortical VOI in the motor area were compared with spectral changes of the identical area.

## Methods

Nine patients with probable or definite early ALS (6 males, 3 females, aged 37 - 68 years, median 55 years) and 10 age matched healthy controls (7 males, 3 females, aged 34 - 67 years, median 57 years) were investigated at an 1.5 whole body system. A diffusion weighted single shot EPI sequence with diffusion sensitised gradients in six directions (TR 250ms, TE 100ms, b-value 1200s/mm$^2$, slice thickness 3mm, number of slices 19, FOV 230mm, matrix 128$^2$, 7 averages) was applied. Maps of fractional anisotropy (FA maps) were created by using the SPM99 diffusion toolbox. A voxel based analysis was performed according to a specified optimised protocol for voxel based morphometry [4] by using SPM99 and only performing affine transformations. To exclude voxels of grey matter and subcortical grey matter, the FA images were masked with a cut-off below 0.4. A one-sided *t*-test was performed (healthy –ALS), the significance level was chosen at $p<0.05$, corrected for multiple comparisons. A single voxel PRESS sequence (TR 3,000 ms, TE 30 ms, 80 acquisitions, 8 ml VOI, acquisition bandwidth 1000 Hz) was applied in the motor area (MA) of all subjects. Absolute quantitation and a correction for the amount of CSF within the VOI were performed. The spectroscopic volume of interest was additionally evaluated in respect of the local FA, see Figure 2.

## Results

Using voxel based morphometry, the FA of the corticospinal tract (CST) in the region of the semiovale center was significantly reduced in ALS, Figure 1. Using the ROI evaluation of the spectroscopic VOI (Figure 2), the mean FA was the same for the patients and the controls, Table 1. N-acetyl-aspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (Ins), and glutamine & glutamate (Glx) were not different between ALS patients and controls, Table 1. NAA was not correlated with the FA.

## Discussion

Changes of the diffusion characteristics within the CST in ALS detected by a region-of-interest analysis have previously been described [1,2]. Using a voxel based analysis, no a priori hypothesis has been assumed in our study. In early ALS, only the superior part of the CST is affected. This finding is prior to any metabolic alterations within the motor area, where also no changes of the FA could be detected. Thus, axonal pathology indicated by a reduced FA, seems to precede the changes in the motor area.

## References

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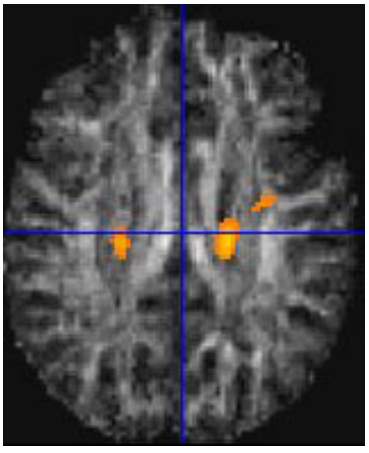

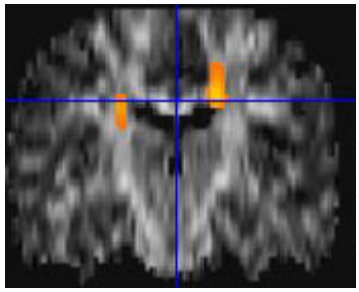

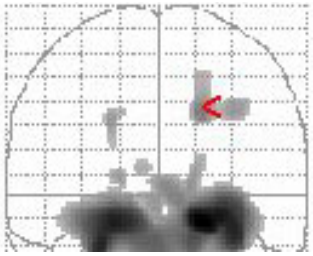

| voxel-level $p_{corrected}$ | $T$ | ($Z_e$) | voxel-level $p_{uncorrected}$ | x,y,z {mm} | | |
|---|---|---|---|---|---|---|
| 0.011 | 5.80 | ( 4.25) | 0.000 | -18 | 32 | -4 |
| 0.013 | 5.72 | ( 4.22) | 0.000 | 18 | 36 | -4 |
| 0.039 | 5.01 | ( 3.88) | 0.000 | 20 | -18 | 38 |

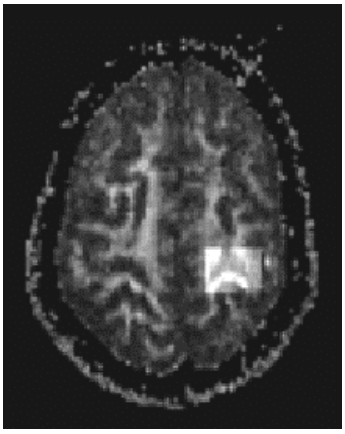

**Figure 1: Differences between the FA of ALS and healthy controls**
The highlighted regions show the significantly different areas of FA between controls and ALS, as tested by a *t*-test (healthy – ALS) and a significance level of $p<0.05$, corrected for multiple comparisons. As an only affine normalisation had been performed, striking effects in the frontobasal area and the orbits were detected. These effects were due to strong distortions of the EPI images in this anatomical region.

**Figure 2**
Voxel position of the spectroscopic VOI. For this region an additional evaluation of the FA was performed.

| | NAA | Cho | Cr | Ins | Glx | FA |
|---|---|---|---|---|---|---|
| ALS | 8.6 (8.1 - 9.0) | 1.4 (1.3 - 1.5) | 5.5 (5.2 - 5.8) | 4.0 (3.8 - 4.2) | 7.5 (6.8 - 8.2) | 0.35 (0.33 - 0.36) |
| Healthy | 9.4 (9.0 - 9.9) | 1.3 (1.2 - 1.5) | 5.4 (51. - 5.6) | 3.9 (3.6 - 4.2) | 8.0 (7.3 - 8.7) | 0.35 (0.32 - 0.38) |

**Table 1: Absolute concentrations of the metabolites and values of FA within the motor area**
The metabolites and the FA were given as mean (confidence interval). The metabolites were given in [mM], the FA is dimensionless. No significant differences were found after correction for multiple tests (Bonferroni).