Brain White Mater Differences Between Normal Subjects and ALS Patients Assessed by Diffusion Tensor Imaging

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Abstract: - Amyotrophic lateral sclerosis (ALS) is characterized by progressive degeneration of motor neurons. A reliable, noninvasive, and objective imaging method of upper motor neuron involvement is critical for the early diagnosis and monitoring of disease progression in ALS patients. Magnetic resonance diffusion tensor imaging (DTI) has been used to show differences in fractional anisotropy (FA) of water diffusion in brain white matter in ALS patients compared to normal controls of the same age group. In this paper, we studied the spatial extent of the brain areas affected in ALS patients using DTI. Our preliminary results show significantly higher FA values in normal subjects compared to ALS patients localized in the left and right frontal and temporal lobes.

Key-Words: Diffusion Tensor Imaging, Fractional Anisotropy, Amyotrophic Lateral Sclerosis, DTI, FA, ALS

1 Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurological disease affecting approximately 1 in 60,000 people in the United States each year. Clinically, ALS is manifested by rapid progression of muscle weakness, atrophy, and spasticity. Pathologically, it is characterized by progressive degeneration of upper and lower motor neurons in the spinal cord, brainstem, and cerebral cortex (Cronin et al 2007). Most ALS patients die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. Unfortunately, there is no cure for this devastating disorder, but certain treatments can improve survival and quality of life (Shoesmith et al 2006). The corticospinal tract connects the cerebral motor cortex with the spinal cord. Damage to these fibers is secondary to upper motor neuron degeneration. Thus, a reliable, noninvasive, and objective imaging method of upper motor neuron involvement is critical for the early diagnosis and monitoring of disease progression in ALS patients.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that allows measuring water diffusion in the living tissue and, in particular, in the white matter of the brain, where the organization of neuronal axons and of their myelin sheaths in parallel bundles promote diffusion of the water molecules preferentially along their main direction (Beaulieu et al 2002). Measuring the location, orientation, and preferential diffusion of the tracts using DTI can indirectly, yet objectively, detect and quantify degeneration of nerve fibers. Molecular diffusion refers to the random Brownian motion of molecules that is due to the thermal energy carried by these molecules. DTI MRI relies on imaging the diffusion of water molecules, which, during their random displacement, probe the structure and geometric organization of tissues at the microscopic scale of several microns, which is well beyond the best resolution of about 1 millimeter offered by regular MRI. DTI is the only noninvasive methodology for observing diffusion in vivo, in both superficial and deep organs, in all three dimensions, and thus allows the study of diffusion differences along preferential directions (Basser et al 1996). Since the MRI signal is sensitive to tissue displacement, diffusion is encoded in the MRI signal using magnetic field gradient pulses, and thus displacements that occur only along the direction of the gradient are visible. The effects of this anisotropic diffusion can be easily detected by measuring variations in diffusion resulting from changing the direction of the gradient pulses.

In the past few years, several studies have shown a reduction in fractional anisotropy (FA), a measure of anisotropic diffusion, in the internal capsule of ALS patients (Jacob et al 2003). In this study, we examined whether DTI MRI can detect

FA changes in other areas of the brain of ALS patients, including the frontal, parietal, temporal, and occipital lobes, and the genu of the corpus callosum, compared to age-matched normal control subjects.

2 Methods

2.1 Diffusion Tensor Imaging

One-dimensional diffusion is fully described by a single (scalar) parameter, the diffusion coefficient, *D*. The attenuation *A* of the MRI signal S_0 due to diffusion is given by $A = e^{-bD}$, where the parameter *b* describes the gradient pulses used in the MRI sequence (Cosottini et al 2005). However, in the presence of anisotropy, diffusion is characterized by a symmetric tensor **D** whose elements D_{ij} describe molecular displacement in the direction *i* when a pulse is applied along the direction *j*, with *i, j = {x, y, z}* (Stejskal et al 2007). This tensor is given by

$$D = \begin{pmatrix} Dxx & Dxy & Dxz \\ Dyx & Dyy & Dyz \\ Dzx & Dzy & Dzz \end{pmatrix}.$$

Thus, the measured MRI signal S_k is given by $S_k = S_0 \cdot \exp(-b_0 \mathbf{g}^T \mathbf{D} \mathbf{g})$, where b_0 and $\boldsymbol{g}$ describe the magnitude and direction of the gradient vector, respectively. In order to obtain unique values for the six unique tensor elements, acquisition of six directionally weighted samples per slice are needed; however, since attenuation of MR signal is calculated relative to a baseline image S_0 acquired with no diffusion encoding, a minimum of seven acquisitions for each slice are actually required.

2.1.1 Fractional anisotropy

Fractional anisotropy (FA) measures the fraction of the magnitude of the tensor that can be ascribed to anisotropic diffusion (Basser et al 1996). Mathematically it is given by the following expression,

$$FA = \sqrt{\frac{3}{2}} \frac{\|D - \langle D \rangle I\|}{\|D\|}, \qquad \begin{matrix} \textbf{2.3.1} \\ \textbf{2.3.2} \\ \textbf{2.3.3} \end{matrix}$$

where <D> is the mean diffusivity and ***I*** the identity matrix. FA takes on values between 0 (perfectly isotropic diffusion) and 1 (infinite cylinder) and is thus directly comparable across different subjects.

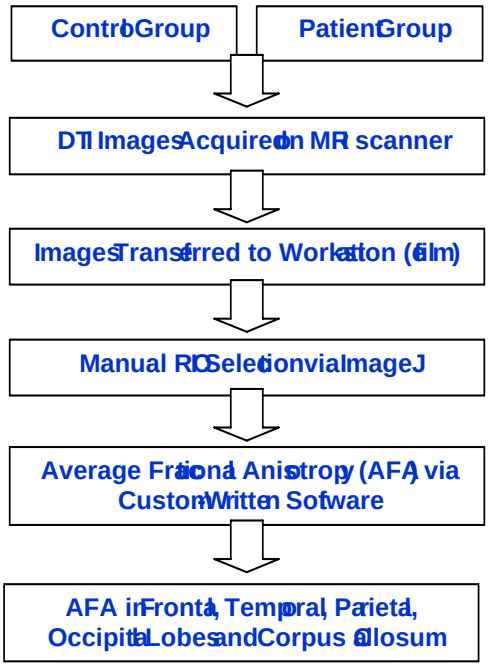

Fig. 1 Outline of the analysis procedure.

2.2 Subjects

Seven subjects participated in this preliminary study, four ALS patients and three normal age-matched controls. Participants completed an extensive and comprehensive battery of clinical and laboratory tests to confirm a diagnosis of ALS based upon El Escorial criteria. Disease staging and progression was scored according to the Appel ALS rating scale, in which the score is the sum of five groups of functional scores: bulbar function, respiration, muscle strength, upper extremity functions, and lower extremity functions. The normal score for each functional group is 6, making 30 the Appel score for a completely normal person. As a patient's condition worsens, the score becomes higher, with 164 as the worse possible score. Additional studies included complete neuropsychological and laboratory assessment, and radiographic and electrodiagnostic testing.

2.3 Procedure

2.3.1. Data Acquisition

Imaging studies were performed on GE 3T Excite HD MRI scanners located at the Department of Radiology at Methodist Hospital. Using a single shot EPI sequence, we acquired consecutive axial slices with no gap (slice thickness 3 mm, b =1000 s/mm^2) covering the entire brain. The imaging

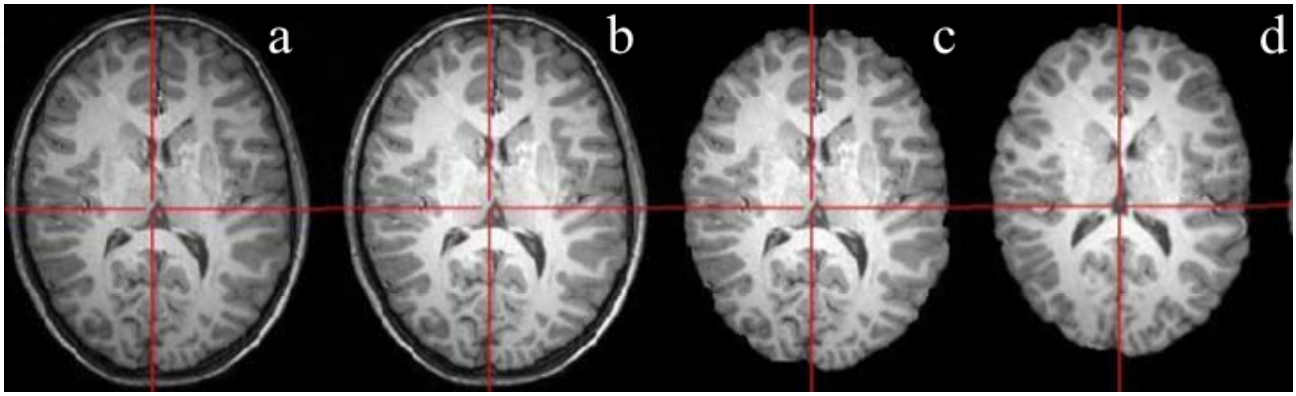

Fig. 2 (a) Original MRI after (b) bias field correction and nonlinear noise reduction, (c) brain extraction, and (d) AC/PC alignment and Talairach transformation.

matrix was 128x128 with a FOV of 220 mm resulting in an in-plane resolution of 1.7 mm x 1.7 mm. For each slice, a total of 16 images were acquired, 15 images with different diffusion-weighted directions and one image without diffusion weighting (b=0) (Karmonik et al 2007). After acquisition, all images were transferred to a workstation for off-line processing. Before further analysis, image quality was checked by requiring a SNR $\geq$ 20 (Hunsche et al 2001) in the DTI images with b = 0, so that DTI parameters could be quantified reliably. The SNR was computed as the ratio of the mean signal intensity in a predefined ROI in the white matter to the standard deviation of the signal intensity in a background ROI outside the brain.

2.3.2 Image Analysis

From those 16 images, the diffusion tensor and FA values were calculated for each voxel, with an algorithm based on single value decomposition. Regions of interest (ROIs) located in the white matter of the temporal, parietal, occipital, and frontal lobes and in the genu of the corpus callosum were manually outlined using only one slice per ROI, and the average value of the FA in these ROIs was determined using an in-house-developed plug-in to the NIH image processing software ImageJ. The entire analysis procedure is outlined in Fig.1.

In parallel with the clinical studies, we have been developing tools to automate the analysis of DTI images. Figure 2 shows an example of an original image (Fig. 2a) and the images obtained after bias field correction and nonlinear noise reduction (Fig. 2b), brain extraction (Fig. 2c), and AC/PC alignment and transformation into Talairach space (Fig. 2d). Our objective is to develop a system with a graphical user interface to accomplish all necessary steps automatically.

Table 1 Comparison of the group of normal subjects with the group of ALS patients.

ROI	*p*-value
R Temporal Lobe	**.000**
L Temporal Lobe	**.002**
R Parietal Lobe	.736
L Parietal Lobe	.652
R Occipital Lobe	.955
L Occipital Lobe	.497
R Frontal Lobe	**.001**
L Frontal Lobe	**.000**
Corpus Callosum	.313

2.3.3 Statistical Analysis

Using the one-tailed unpaired student t-test, the statistical significance of inter-group differences in the average FA values between the ALS patients and the control subjects was determined.

3 Results

Figure 3 shows an example of DTI images acquired from a normal subject (left) and an age-matched ALS patient (right), along with the ROIs selected in the right temporal lobe. Preliminary analysis showed overall higher average FA values in the control group (TL: ALS 0.32±0.02, control 0.41±0.04; PL: ALS 0.34±0.04, control 0.37±0.06; OL: ALS 0.31±0.06 control 0.35±0.06; FL: ALS

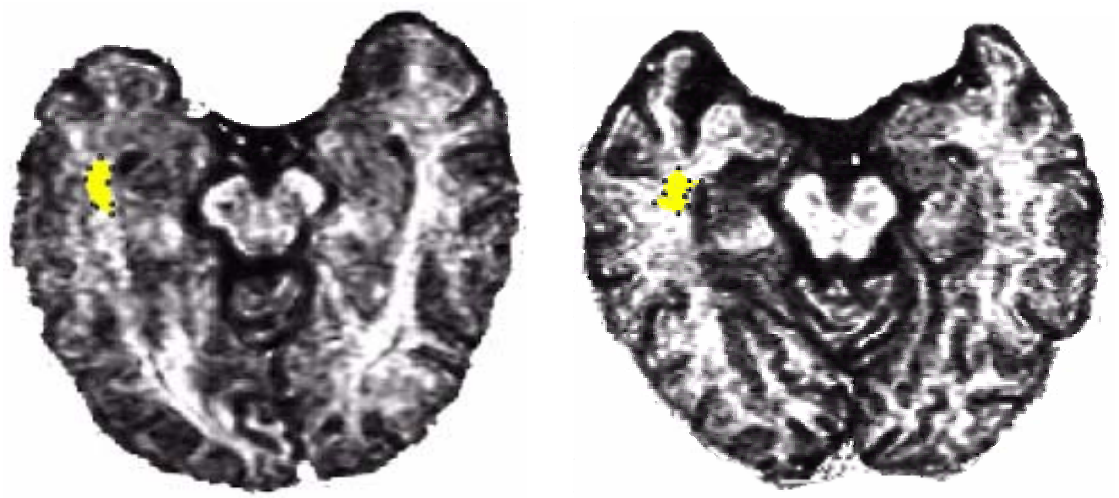

Fig. 3 Example of DTI scans obtained from a normal subject (left) and an ALS patient (right) and the manually outlined ROIs in the left temporal lobe.

0.24±0.02 control 0.30±0.6; GCC: ALS 0.39±0.14 control 0.53±0.03). Statistically significant differences were found only in the left and right temporal lobes ($p<0.002$) and in the frontal lobe ($p=0.012$). Further studies with a larger sample size are, of course, necessary to confirm these preliminary findings.

4 Conclusions

Our first results presented here indicate that statistically significant differences in FA values determined with DTI may exist in ALS patients compared to age-matched controls in the temporal and frontal lobes of both hemispheres. We are currently collecting and analyzing data from a larger population of ALS patients and additional normal subjects which is necessary to confirm the trend we have observed in the first seven subjects of our study. Furthermore, we are developing automated tools that can alleviate the tedious process of manual analysis.

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