Investigating white matter changes in amyotrophic lateral sclerosis using high-dimensional deformable diffusion-tensor image registration

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Introduction: Amyotrophic lateral sclerosis (ALS) is a degenerative disease of motor neurons, whose diagnosis requires evidence of both upper and lower motor neuron dysfunction. Currently, upper motor neuron (UMN) disease is assessed primarily by physical examination, because no objective quantitative test is widely available for clinical use. Several groups have reported the efficacy of diffusion tensor imaging (DTI) to evaluate the white matter tracts in the brain as a surrogate marker of UMN disease, specifically finding reduced fractional anisotropy (FA) in the corticospinal tracts. In this study, we evaluated the use of a high-dimensional DTI normalization algorithm to detect the location and magnitude of FA changes in patients with ALS.

Materials/Methods: Eight ALS patients along with eight age-matched healthy controls were recruited. Magnetic resonance imaging was performed on a 3.0-T Siemens Trio scanner. For each subject, diffusion tensor imaging was performed using a single-shot, spin-echo, diffusion-weighted echo-planar imaging (EPI) sequence. The diffusion sampling scheme was as follows: one image without diffusion gradients ($b = 0$ s/mm^2), followed by twelve images measured with twelve non-collinear and non-coplanar diffusion encoding directions isotropically distributed in space ($b = 1000$ s/mm^2). Additional imaging parameters for the diffusion-weighted sequence were: TR = 6500 ms, TE = 99 ms, 90^o flip angle, number of averages = 6, matrix size = 128 × 128, slice thickness = 3.0 mm, spacing between slices = 3.0 mm, 40 axial slices with in-plane resolution of 1.72 × 1.72 mm.

Diffusion-tensor images were spatially normalized using a novel high-dimensional deformable registration algorithm that explicitly optimizes tensor orientation for optimal alignment of white matter structures [1]. A population-specific tensor template was generated from the 16 subject images using the following iterative process. An initial template was computed as an average of the original subject images, to which the subjects were first registered. The normalized images were subsequently averaged to produce an improved template, which was then used as the target for the next iteration. This procedure was repeated until the change between templates from consecutive iterations became sufficiently small.

FA maps were subsequently derived from the normalized diffusion-tensor images. Statistical parametric mapping was applied to these maps for statistical inference on a voxel-by-voxel basis using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) [2]. We carried out both the "control minus ALS" and the "ALS minus control" analyses. The clusters that we report were those that exceeded the extent threshold of 10 voxels and the corrected p-value threshold of 0.05 at cluster-level.

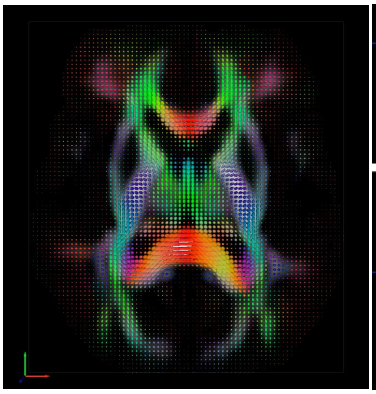

Figure 1: population-specific template derived from subjects

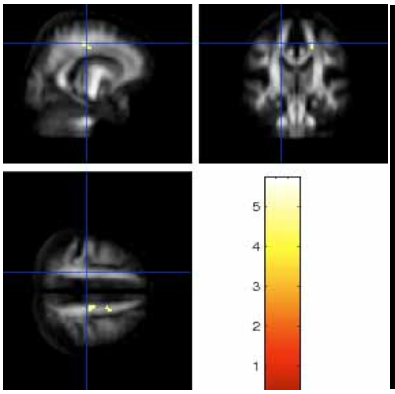

Figure 2: statistically significant clusters (control > ALS) overlaid with the FA map derived from the template

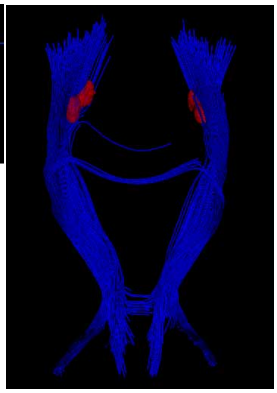

Figure 3: statistically significant clusters overlaid with the corticospinal tracts derived from the template

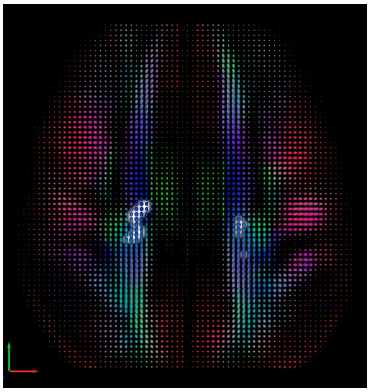

Figure 4: statistically significant clusters overlaid with the template

Results: The DTI normalization procedure successfully converged in four iterations. A representative slice of the color-coded tensor glyph from the population-specific DTI template derived during the procedure is shown in Figure 1, using the standard coloring scheme of the principal eigendirection (red=transverse, blue=craniocaudal, green=anteroposterior). The size of the tensor glyph in each voxel is scaled by the corresponding FA value. Figure 2 displays the output from SPM, showing significant clusters with reduced FA values in ALS subjects in the bilateral centrum semiovale corresponding to the expected locations of the corticospinal tract. These clusters were highly significant (cluster 1:P=0.000, size=49 (voxels), cluster 2:P=0.025, size=13, cluster 3:P=0.025, size=13). Figure 3 shows these clusters overlaid on the corticospinal tracts derived by applying tractography methods to the DTI template, establishing precise localization of these clusters to these tracts. Figure 4 shows the clusters overlaid on the template directly. No significant clusters were found with increased FA values in ALS subjects.

Discussion: In this preliminary study, we successfully applied a high-dimensional DTI normalization algorithm to 12-direction DTI data. The robustness of our methodology is demonstrated by the fact that the only areas of significantly reduced FA in the entire volumetric DTI dataset were located in the corticospinal tracts; moreover, the magnitude of these FA reductions were highly significant. The high accuracy of the normalization process allowed us to omit the usual smoothing step from the statistical analysis, thereby improving spatial specificity and probably increasing the significance levels of the differences found. As a further demonstrable benefit of the DTI normalization procedure, by applying tractography methods to the derived DTI template, we were able to localize the abnormalities precisely to the corticospinal tracts. In the future, we hope to apply these techniques in order to develop an MR-based biomarker of UMN disease in ALS patients, for potential use in early disease detection, monitoring of disease progression, and development of future treatments.

References:

[1] Zhang et al, Deformable registration of diffusion tensor MR images with explicit orientation optimization, Med Imag Anal, 2006

[2] Friston and Holmes, Statistical parametric maps in functional imaging: a general linear approach. Human Brain Mapping, 1995