Whole-tract reduction in fractional anisotropy in the corticospinal tracts of amyotrophic lateral sclerosis patients, as measured using a weighted 3-D region of interest in template space after deformable diffusion tensor imaging registration

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Purpose: To determine if a whole-tract measure of fractional anisotropy in the corticospinal tract is significantly reduced in amyotrophic lateral sclerosis.

Introduction: Amyotrophic lateral sclerosis (ALS) is a degenerative disease of motor neurons. Diffusion tensor imaging (DTI) measurements in the corticospinal tract (CST) of patients with ALS have shown local reductions in fractional anisotropy (FA), thought to reflect degeneration of the upper motor neuron axons. Regions-of-interest (ROI) measurements can be time-consuming if they require user interaction to define the ROIs, whether by manual segmentation or fiber tractography. In this study, we performed whole-tract (global) CST measurements of FA, using a deformable tensor-driven registration algorithm that warps individual DTI data into a common spatial frame ("template space"), and a 3-D ROI of the CST constructed in template space. This registration algorithm is fully automated in that it requires no user segmentation or identification of anatomical landmarks.

Materials/Methods: Twelve ALS patients (ages 31-76; mean 61) and seven healthy controls (ages 57-67; mean 63) were recruited into the study. Diffusion tensor imaging was performed on a 3.0T Siemens Trio scanner using an 8-channel coil and a single-shot spin-echo diffusion-weighted echo-planar imaging (EPI) sequence, with a GRAPPA acceleration factor of 3. The diffusion sampling scheme consisted of 4 images without diffusion gradients (b=0 s/mm^2) and 30 measured with non-collinear/non-coplanar diffusion encoding directions isotropically distributed in space (b = 1000 s/mm^2). This pulse sequence was repeated for a total of 3 (NEX=3) measurements. Other parameters: TR=6700 ms, TE=85 ms, FOV=245x245 mm, matrix=112x112, slice 2.2 mm, gap 0 mm, voxel dimension 2.19x2.19x2.2 mm^3, total scan time: 13 minutes.

Diffusion tensor images were spatially normalized using a 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 19 subject images using an iterative alternating process of averaging and registration, using three successive transforms – first rigid, then affine, and finally a hierarchical piecewise affine transformation (i.e. diffeomorphic). For the rigid and affine transforms, this iterative process was repeated 3 times; for the diffeomorphic transform, the procedure was repeated until the change between templates from consecutive iterations became sufficiently small.

The weighted 3-D ROI corresponding to the CST was constructed in template space by the following procedure. For each of the seven control subjects, voxels corresponding to the CST were determined using DTIStudio [2], which uses the Fiber Assignment by Continuous Tracking (FACT) algorithm [3]. Two regions-of-interest were placed in the cerebral peduncle and the white matter beneath the primary motor cortex, as previously described by Wakana et al [4], and the "cut" operation was performed. Resulting voxels were saved as binary masks, to which the spatial transforms determined by the above DTI normalization procedure were then applied. The transformed masks were averaged in template space to generate the weighted 3-D ROI, scaled so that the sum of weights across all ROI voxels equaled 1. For each individual, template-space FA was calculated directly from the transformed tensors, and the whole-tract (global) measure of FA was measured by the weighted average of the transformed FA values over the 3-D ROI. A similar ROI was constructed of the forceps minor (frontal projection of the corpus callosum), in which whole-tract measurements of FA were also performed as a control.

Results: The diffeomorphic registration converged in 6 iterations. Whole-tract FA measurements were significantly different in groups of ALS patients and controls (Mann-Whitney-U, Z = -2.958; p = 0.003) (see boxplot, lower right). There was no difference in whole-tract measurements of FA in the forceps minor (Mann-Whitney-U, Z = -0.761, p = 0.447).

Discussion: We found a highly significant but CST-specific decrease in whole-tract FA in ALS. Because the registration algorithm requires no user input, this measurement method would be easier and less time-consuming to apply to large groups of data. Moreover, the use of a single summary measurement such as whole-tract FA is attractive for several other reasons: (1) it avoids the multiple-comparison problems that complicate the statistical analysis of voxel-based methods, and (2) it would be easier to use as a quantitative biomarker. Finally, (3) unless particular areas of the CST are more prone than others to undergo degeneration in ALS, an unproven hypothesis, the methodology of looking for specific regional abnormalities common to a population of patients seems unjustified. More likely, disruptions occur in a random and widespread fashion throughout the tract, inasmuch as the disease can manifest in a variety of clinical presentations. Therefore, a whole-tract measurement of axonal degeneration seems more appropriate.

References: [1] Zhang et al, IEEE Trans Med Imaging. 2007 Nov;26(11):1585-97. [2] Jiang et al, Comput Methods Programs Biomed 2006; 81:106-116. [3] Mori et al, Neurol 1999; 45:265-9. [4] Wakana et al, Neuroimage 2007; 36:630-44.

Figure (below). Left: color-coded map of the principal eigenvector of the tensor template (coronal section). Middle: weighted ROI defining the CST on same coronal section. Right: Fusion image. Note: only one coronal image is shown of 3-D data. **Graph** (right). Box plot distributions of whole-tract FA in CST (blue) and forceps minor (red), in ALS (left) and controls (right). Difference is significant in CST (p=0.003).