Application of automated fiber tract identification and Restriction Spectrum Imaging to study microstructural changes in white matter tracts associated with temporal lobe epilepsy.

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Introduction

Diffusion Imaging (DI) is being increasingly used to study a variety of diseases and disorders. Diffusion of water perpendicular to white matter fibers is highly restricted, and so DI can be used to infer their orientations. DI has also been used to derive measures that indicate the location of disease-related differences in tissue properties. For example, FA, a measure derived from diffusion tensor (DT) calculations, describes the degree to which diffusion rates along three orthogonal axes are different from each other. A decrease in FA relative to normal controls for clinical populations is often used as a measure of white matter integrity. Changes in FA, however, could result from a number of factors, including changes in the distribution of fiber orientations or in the fraction of free water in a given voxel. Alternatives to DT analysis have recently been developed, including the use of spherical deconvolution or multiple volume fractions to model isotropic diffusion as well as diffusion along two or more fiber bundles with different orientations. We have used this type of multi-compartment model to derive new diffusion measures to study differences in tissue properties associated with temporal lobe epilepsy (TLE).

Methods

Some of the data used in this study were included in our recent description of a probabilistic-atlas based method for automated identification of white matter fiber tracts; detailed descriptions of the procedures for subject recruitment, data collection, image pre-processing, and tract identification can be found there [1]. Briefly, MRI data were collected on a GE 1.5T EXCITE HD scanner with an 8-channel head coil. Two DI volume series were acquired with 6 diffusion gradient directions using b-values of 100 and 300 s/mm^2, and three were acquired with 51 directions using b-values of 600, 800, and 1000 s/mm^2, each with an additional b=0 volume. All participants provided written consent prior to enrollment in the study, which was approved by the Institutional Review Board. 41 healthy control subjects, 10 left TLE (temporal lobe epilepsy) patients, and 12 right TLE patients were included in the current study.

Diffusion tensors were calculated using linear inversion after taking the log of the data, thus performing a monoexponential fit across the five b-values, constrained by the 5 b=0 volumes and 165 DI volumes. To account for the rotations required for correcting head motion, the diffusion gradient vectors used by the diffusion pulse sequence were adjusted with the rotational component of the motion correction transformation matrices. Tensor fits were used to derive DT measures including FA (fractional anisotropy), MD (mean diffusivity), D_L (longitudinal diffusion), and D_T (transverse diffusion).

Restriction Spectrum Imaging was used to estimate diffusion in multiple compartments with varying levels of restriction. Highly restricted diffusion was modeled with a FOD (fiber orientation distribution) using 4th order spherical harmonics, assuming $D_L = 10^{-3}$ mm^2/s, and $D_T = 10^{-5}$ mm^2/s. Isotropic tissue was modeled with $D_L = D_T = 10^{-3}$ mm^2/s. Isotropic free water (i.e. CSF) was modeled with $D_L = D_T = 2x10^{-3}$ mm^2/s. Derived measures were isoFW (isotropic free water volume fraction), isoTs (isotropic tissue volume fraction), FOD_{L0} (restricted tissue volume fraction; i.e. L=0 spherical harmonic component), FOD_{L2} (norm of L=2 spherical harmonic components), and FOD_{L4} (norm of L=4 spherical harmonic components).

White matter fiber tract ROIs (Fig. 1) were created using individual subjects' T1-weighted images and diffusion data with a probabilistic fiber atlas [1]. The fiber atlas consists of averaged information about the locations and local orientations of the chosen fiber tracts. T_1-weighted images were used to map the brain into a common space and DT orientation estimates were compared to the atlas to obtain a relative probability that a voxel belongs to a particular fiber given the similarity of diffusion orientations. These fiber probability maps were used to calculate weighted averages of DT and FOD derived measures.

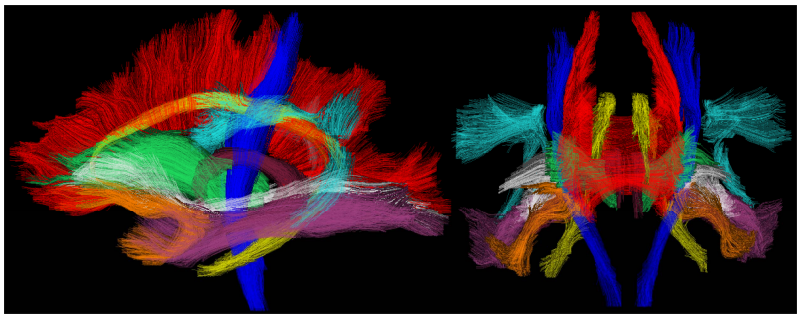

Figure 1. Automatically generated fiber tract ROIs for an individual control subject, from left sagittal and anterior coronal views.

Results

Widespread reductions of FA in white matter fiber tracts were found in TLE patients relative to healthy controls; significant group effects (ANCOVA, $p<0.01$) were found in several fiber tracts, including bilateral parahippocampal cingulum (Fig. 2A). Differences in MD, D_L, and D_T were not significant. By using a multi-compartment FOD model, we derived a measure FOD_{L2} that showed a similar pattern of widespread reductions in white matter fiber tracts. Effect sizes were slightly increased, as were ANCOVA F-statistics, such that several additional fibers were revealed to be significantly affected by temporal lobe epilepsy (Fig. 2B). We did not find significant changes in the volume fractions corresponding to fast isotropic diffusion (i.e. CSF), slower isotropic diffusion (i.e. tissue), or restricted diffusion (i.e. fibers). Similar to FOD_{L2}, significant differences in FOD_{L4} were found in several fiber tracts. We did not, however, find significant differences in the ratio of these two measures, which has been proposed as a measure of the degree of crossing fibers.

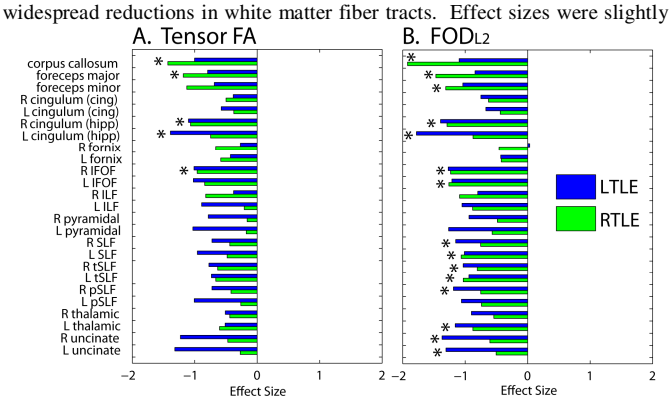

Figure 2. Effect sizes (Cohen's d) for fiber tract ROI differences in tensor FA and FOD_{L2} measures between controls and LTLE or RTLE patients. Asterisks indicate $p<0.01$, one-way ANCOVA between the three groups separately for each fiber, with age as regressor.

Discussion

Similar to FA, FOD_{L2} is a measure of coherence of fiber orientations, but multi-compartment FOD fitting accounts for potentially confounding factors including free water and isotropic tissue. This resulted in a more sensitive and specific measure of the microstructural changes in white matter fiber tracts that accompany TLE. To further probe the size scales involved in disease related changes, this method can be extended by modeling additional compartments with varying levels of restriction perpendicular to fiber orientations. Although we did not find TLE-related changes in the relative volume fractions of free water, isotropic tissue, and restricted tissue, these measures may be useful in other applications. We also did not find evidence of differences in crossing fibers, but higher b-values may be required to obtain an accurate measure of this.

References

1. Hagler, D.J., Jr., et al., *Automated white-matter tractography using a probabilistic diffusion tensor atlas: Application to temporal lobe epilepsy.* Hum Brain Mapp, 2008.