Semi-automated Fiber-based Analysis of Group Differences in DTI

L. R. Arlinghaus[1], R. Li[2], B. M. Dawant[2], Z. Ding[3], J. Lee[4], S. Park[4], A. W. Anderson[1,3]

[1]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, United States, [2]Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, United States, [3]Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States, [4]Department of Psychology and The Center for Integrative and Cognitive Neuroscience, Vanderbilt University, Nashville, TN, United States

Introduction: Fiber-based (FB) methods of analyzing DTI data offer an alternative to the commonly used region of interest (ROI) and voxel-based (VB) methods. However, they may not be feasible for use in large group studies of multiple white matter (WM) tracts of interest. The FB methods that have been used to date [1-4] require manual seed point definition for fiber tracking, which becomes extremely time-consuming for large studies. A more difficult challenge FB methods face is the definition of point correspondence between fiber bundles of different subjects. Early FB methods did not account for inter-subject anatomic variability [1,2], and more recent methods are tract-specific [3,4]. Proposed here is a semi-automated FB analysis method which utilizes inter-subject image registration to simplify seed point selection and provide guidelines for determining point correspondence between subjects in multiple WM tracts of interest. This method was used to investigate fractional anisotropy (FA) differences between control (CO) and schizophrenic (SZ) subjects in three sets of WM tracts previously implicated in schizophrenia: the right and left cingulum, arcuate, and uncinate fasciculi. ROI and VB analysis of the FA maps were also performed for comparison.

Methods: Data sets were collected from eight healthy CO and five SZ outpatients on a Philips Intera Achieva 3T MRI scanner. The DTI data sets were acquired with a single-shot SE EPI sequence with 92 diffusion directions (b = 1000 s/mm^2). Whole-brain coverage was provided with 55 slices (2.5 mm isotropic voxels) and matrix size 96 x 96. Two high-resolution anatomical data sets were also collected for use in inter-subject image registration: a 3D T1-weighted TFE (turbo field echo) and a T2-weighted TSE (turbo spin echo), which was slice-matched to the DTI data. Motion-correction and tensor calculation were performed using Philips Research Integrated Development Environment (PRIDE) software. Data from one CO subject was selected for use as the target (TARG) image for image registration. The FA maps of each subject were co-registered to the TARG FA maps via a single transformation which was calculated from a set of intra- and inter-subject registrations [5-7] of the non-diffusion-weighted images (b = 0) and the anatomical data sets. Seed points for fiber tracking were selected in two locations along each WM tract of interest in the target FA maps. These coordinates were then transformed to each subject's DTI space and expanded to spherical seed regions with a radius of 5 voxels to compensate for small errors in registration. Tracking was performed using the PRIDE Fiber Tracking tool (v6.0a1) with a multi-ROI approach, an FA threshold of 0.25, and a direction threshold of 0.85 (cingulum) and 0.75 (uncinate and arcuate). The medial axis of each bundle was calculated [8] such that the points defining it corresponded across subjects. The spacing of subsequent points along the axis was scaled by the ratio of the mean fiber length between seed regions of the subject's bundle and the TARG bundle, so that the number of points defined along each subject's bundle remained constant, regardless of the total bundle length. FA values of corresponding locations along each tract were averaged across groups and compared at each point. VB analysis of the co-registered FA maps were also performed for comparison, and ROI analysis was performed in the regions where statistically significant differences were detected by both the FB and VB methods. Statistical analysis of all three methods was performed using a t-test.

Results: Fiber bundles were successfully tracked in each of the TARG, CO, and SZ data sets except for the right cingulum in SZ3 and the right arcuate in SZ1. FB analysis suggested differences in FA between the CO and SZ groups in two of the six fiber bundles: the temporal portion of the right uncinate (decreased FA value in the SZ group compared to the CO group with $p<0.13$) and the left arcuate (increased FA in the SZ group compared to the CO group with $p<0.09$). Both ROI and VB analysis of the corresponding regions of WM showed statistically significant differences in FA values ($p<0.05$).

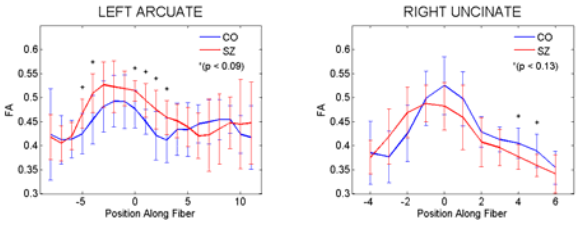

Fig. 1 Mean FA values for the CO and SZ groups plotted as a function of their position along the bundle from the frontal lobe to temporal lobe. Statistical trends toward differences (*) and the standard deviation (error bars) of the FA values are also shown.

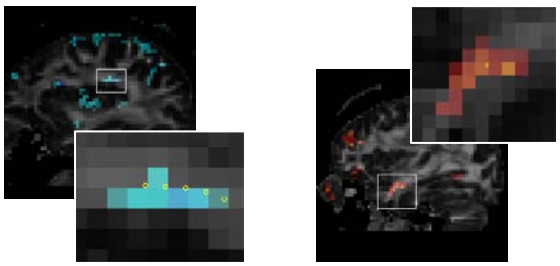

Fig. 2 Left: VB results showing SZ>CO FA (blue voxels) in the left arcuate. Right: VB results showing of CO>SZ FA (red voxels) in the right uncinate. Yellow circles represent points along the medial axis of the fiber bundle in that plane.

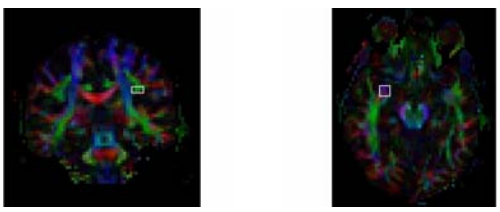

Fig. 3 Examples of the ROI placement for the left arcuate and the right uncinate, respectively.

Discussion: The FB analysis method proposed here has several advantages over ROI and VB methods. First, ROI methods are time consuming and prone to intra- and inter-rater error. The semi-automated seed selection scheme demonstrated here performed well and significantly decreased user interaction. Second, both ROI and VB methods are susceptible to errors due to partial volume averaging with fiber tracts running in parallel with the tract of interest and with gray matter or CSF. This is limited in FB methods by isolating the WM tract of interest before analysis is performed. (It should be noted, however, that there is a potential for overestimating diffusion parameters along the isolated bundles when a minimum FA value is used as a stop criterion in fiber tracking.) Third, accurate co-registration of images is a difficult task because of inter-subject anatomic variability. The methods proposed here utilized image co-registration, while accommodating minor registration errors. A limitation of the method used to determine point correspondence is that it only allows for examination of the portion of the fiber bundles located between the seed regions. The trends in the FB analysis were consistent with the result of both the VB and ROI analyses. The decreased sensitivity of the FB method is most likely a result of the differences in sample size used to calculate the mean FA of a region in each method. The FB method calculates average FA values from the cross-section of the fiber bundle, which may only consist of 4 or 5 voxels. The ROIs used in this study ranged from 10 to 20 voxels in size, and only clusters of 20 or more voxels with $p<0.1$ were considered in the VB analysis. Our finding of decreased FA in the right uncinate fasciculus of the SZ group was consistent with results reported by others [9], and our finding of increased FA in the left arcuate of the SZ group was mostly likely due to a bias introduced by two of the SZ subjects who experience auditory hallucinations, which would be consistent with results reported previously [10]. The consistency with other analysis methods and results reported by others suggest that this method may be of use in large DTI studies. Future work includes applying this method to extreme cases of anatomical inter-subject variability and to additional data sets.

References: [1] Mori, S., *et al.* Magn Reson Med, 2002. 47(2): p. 215-23. [2] Fillard, P., *et al.* Lecture notes in computer science, 2003(2879): p. 16-23. [3] Gong, G., *et al.* Hum Brain Mapp, 2005. 24(2): p. 92-8. [4] Partridge, S.C., *et al.* J Magn Reson Imaging, 2005. 22(4): p. 467-74. [5] Maes, F., *et al.* IEEE Trans Med Imaging, 1997. **16**(2): p. 187-98. [6] Li, R. MS Thesis in EECS. 2001, Vanderbilt University: Nashville, TN. [7] Rohde, G.K., *et al.* IEEE Trans Med Imaging, 2003. **22**(11): p. 1470-9. [8] Ding, Z., *et al.* Magn Reson Med, 2003. 49(4): p. 716-21. [9] Kubicki, M., *et al.* J Psychiatr Res, 2005. [10] Hubl, D., *et al.* Arch Gen Psychiatry, 2004. 61(7): p. 658-68.

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