Fiber Geometry and its Relationship to Fractional Anisotropy in the Genu of Patients with Schizophrenia

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Background

Diffusion Tensor Imaging (DTI) is a form of MR imaging that has been used to evaluate white matter pathology in schizophrenia. It has now often been shown with DTI that patients with schizophrenia have reduced Fractional Anisotropy (FA) in many regions of the brain, including the genu of the corpus callosum. The traditional view of FA is that a lower value represents structural damage to the neurons of the tract, such as through the myelin in demyelination or dysmyelination, or damage to the axolemma itself. Such damage would increase the ability of water to diffuse out of the axon, perpendicular to the tract, thereby decreasing the anisotropy. This would support the conclusion that schizophrenia causes problems in the myelination of patient’s neurons. Other explanations taking into account the geometry of the bundle, such as its tortuosity or degree of fanning, are only now being explored, however. Higher fanning of a tract should also lead to a lowered FA, since as the main direction of diffusion of healthy fiber bundles begin to diverge, their group anisotropy will drop.

In the present study, we use a recently developed DTI scalar measure called Shape Normalized Dispersion (SHD) to examine the differences between patients with schizophrenia and normal controls. SHD is a measure looking at the nearby fanning of a structure, computed by analyzing local variation in tensor orientation (Fig. 2, Fig. 3). By performing standard streamline tractography seeded in the genu of the corpus callosum of patients and controls, we were able to extract SHD values from these regions to measure the relative degree of fanning in the two populations, and compared the results to the traditional FA metric.

Methods

- A 3T GE magnet was used to obtain scans from 26 male subjects with schizophrenia, determined by DSM-IV, and 23 normal controls, matched on age, handedness, PSES, and pre-morbid IQ.
- DTI Scan Parameters: Fifty-one directions, TR 17000 ms, TE 78 ms, FOV 24 cm, 144x144 matrix, 1.7 mm slice thickness, 85 axial slices.
- Extra-cerebral voxels were removed through an automated process, followed by deterministic tractography seeded in every voxel where Westin’s Linear Anisotropy measure (CL) was greater than 0.3. Tracking was concluded where CL dropped below 0.15. The tracts were then analyzed to generate 200 individual clusters with similar shape characteristics. Here, each of the 200 fiber bundles has been labeled with a unique color.
- SHD outlier removed from analysis again, the results were similarly significant (t(46)=2.537, p=.015, not shown).

Results

Our analysis revealed depressed FA in the genu of our subjects with schizophrenia relative to our normal controls (t(47)=2.237, p=.030, Fig. 4a). Similarly, when examining SHD, the schizophrenia patients revealed significantly lower SHD in the genu than our control subjects (t(47)=2.796, p=.007, Fig. 4b). There was one obvious outlier in our SHD results, and our results remained significant when this subject was removed from the analysis(t(46)=2.537, p=.015, not shown).

We also performed a linear regression, which revealed that changes in subjects SHD could significantly account for 12% of the change in FA, across groups (r²=0.120, β=-.346, F(1,48)=6.412, p=.015, Fig. 4c). With the SHD outlier removed from analysis again, the results were similarly significant (r²=0.126, β=-.381, F(1,47)=7.788, p=.008, not shown).

Discussion

Both SHD and FA were found to be reduced in the genu of patients with schizophrenia compared to normal controls. The SHD findings, when considered in light of the coincident finding that a significant portion (12%) of variation in FA can be accounted for by changes in SHD, suggest both that schizophrenic patients exhibit white matter geometry abnormalities, and that these abnormalities can partially explain the oft-seen reductions in FA.

The most frequent explanation for these commonly seen reductions in FA amongst patients with schizophrenia is damage to the axon membrane or to the myelin surrounding it. However, the results of our experiment make a compelling case for a possibly coinciding phenomenon of geometric abnormalities in the examined fiber bundles leading to the drop in average FA.

The curvature of the genu led us to choose it for analysis of geometric fanning because SHD outlier removed from analysis again, the results were similarly significant (t(46)=2.537, p=.015, not shown).