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# White matter diffusivity and microarchitecture among schizophrenia subjects and first-degree relatives

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ABSTRACT

*Background:* Impairments in structural and functional connections are demonstrated in schizophrenia. Certain disconnectional patterns may be biomarkers of elevated risk for schizophrenia. Convergent examination of multiple diffusion parameters and cognitive performance better illustrates pathophysiological significance of such disconnectional patterns.
*Methods:* Diffusion Tensor Imaging data on 39 early-course schizophrenia subjects, 21 adolescent/young adult first-degree relatives (FDR) of schizophrenia subjects and 29 healthy controls (HC) were examined for threshold-free clusters of fractional anisotropy (FA) and radial diffusivity (RD) differences correcting for multiple comparisons. Regression models examined the variance contributed by anisotropy differences, age and sex. Group-wise differences on sustained attention, verbal memory and executive functions were examined and correlated with diffusivity measures controlling for age and sex.
*Results:* Schizophrenia subjects showed significantly decreased FA and increased RD in the forceps minor and superior longitudinal fasciculus (SLF) compared to HC. FDR showed decreased forceps minor FA compared to HC, and decreased SLF RD compared to HC and schizophrenia subjects. Quantitative RD differences were 2–3 fold higher compared to FA. Besides, forceps minor RD was inversely correlated with sustained attention in schizophrenia.
*Conclusions:* Schizophrenia and FDR subjects show different patterns of white matter diffusivity compared to HC. While forceps minor changes may be a disease marker, SLF changes may be risk markers. In addition, RD may be a more robust risk marker than FA.



## 1. Background

Schizophrenia is proposed as a 'disconnection syndrome' (Friston and Frith, 1995). Systematic mapping of the 'disconnection' could elucidate pathophysiology, risk for psychoses and endophenotypes. Diffusion tensor imaging (DTI) is a promising non-invasive approach to characterize anisotropy of water diffusion reflecting tissue microstructure. DTI relies on the principle that water tends to diffuse more freely along the longitudinal axis ($\lambda_1$) than along the transverse axes ($\lambda_2$ and $\lambda_3$) of axons. Fractional anisotropy (FA; relative changes in diffusion along the $\lambda_1$ compared to $\lambda_2$ and $\lambda_3$) and radial diffusivity (RD; mean diffusion perpendicular to the axonal orientation) are frequently used to characterize altered anisotropy (Beaulieu, 2002), myelination (Kubicki et al., 2005; Klawiter et al., 2011) and tract coherence (Kubicki et al., 2005). Altered FA alone does not clearly depict changes in white matter microarchitecture. Simultaneously examining multiple diffusivity measures more clearly suggest white matter pathology (Hasan, 2006).

Functional and DTI studies suggest 'disconnected' networks among schizophrenia subjects and first-degree relatives of schizophrenia subjects (FDR) who have about 10% risk for schizophrenia (Gottesman, 1991) compared to healthy controls (HC). Increased prefrontal and thalamic activations during episodic memory processing among schizophrenia subjects and FDR compared to HC suggest an impaired fronto-temporal and fronto-thalamic connectivity (Stolz et al., 2012). Resting fMRI studies report altered functional connectivity among schizophrenia subjects and FDR (Whitfield-Gabrieli and Ford, 2012). DTI studies report altered anisotropy in the association (superior longitudinal fasciculus (SLF), uncinate fasciculus) (Friedman et al., 2008), commissural (corpus callosum, forceps minor) (Friedman et al., 2008) and projection (internal capsule and cingulum) (Ellison-Wright and Bullmore, 2009) fibers in schizophrenia compared to controls. A combined structural and functional connectivity study showed lower coherence between

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the two although there was globally decreased anatomical connectivity (Skudlarski et al., 2010). The nature of diffusivity differences suggests that schizophrenia subjects in general show decreased FA (Bora et al., 2011; Fitzsimmons et al., 2013) and increased mean diffusivity (Fitzsimmons et al., 2013) that may be contributed by increased RD but not axial diffusivity (Seal et al., 2008; Scheel et al., 2013). Anisotropy differences among FDR were intermediate between schizophrenia and HC (Skudlarski et al., 2013). Decreased FA in the SLF among ultra-high risk (UHR) subjects at baseline (Karlsgodt et al., 2009) and in those who later developed psychosis (Bloemen et al., 2010) suggest that reduced anisotropy in the SLF may be a biomarker of risk for psychosis. Another DTI study on UHR subjects reported decreased FA and increased RD among UHR subjects compared to HC in the SLF along with other regions; progressive reduction in FA in the frontal white matter was noted among UHR subjects who later developed psychosis compared to those who did not suggesting that the frontal white matter may also be a risk biomarker (Carletti et al., 2012). It is unclear whether the nature of changes in diffusivity patterns or variations in specific tracts among the diagnostic groups contributes to the heterogeneity of the disorder.

We comprehensively examined multiple diffusivity measures among early-course schizophrenia subjects, FDR and HC. We hypothesized that the: (a) fronto-temporal, fronto-parietal and fronto-thalamic tracts would show reduced FA and increased RD within the same regions among schizophrenia subjects compared to HC, (b) FA and RD in the above tracts among FDR subjects would be intermediate between that of schizophrenia and HC subjects, and (c) diffusivity differences in these tracts would correlate with cognitive performance.

## 2. Methods

### 2.1. Clinical

We enrolled 89 adolescents/young adults with early-course schizophrenia/schizoaffective disorder ($n = 39$), FDR of schizophrenia/schizoaffective disorder subjects ($n = 21$) and HC ($n = 29$) at the University of Pittsburgh, Pittsburgh, PA. FDR had at least one parent/sibling with DSM-IV schizophrenia/schizoaffective disorder who were not participants in this study. Consensus diagnosis was made by collating data from the Structured Clinical Interview for DSM-IV (SCID) (First, 1997), follow-up evaluations and medical charts. Substance abuse in the previous month or dependence 6 months prior to enrolment, mental retardation per DSM-IV, serious neurological (e.g. epilepsy, encephalitis/meningitis) or medical illnesses were exclusion criteria. After fully explaining the experimental procedures, subjects provided informed consents. The University of Pittsburgh IRB approved the study.

Sustained attention, executive functions and verbal memory were evaluated within a week of imaging using the Continuous Performance Test (CPT-IP) (Cornblatt and Keilp, 1994), the Wisconsin Card Sorting Test (WCST) (Berg, 1948) and the Word List Memory Test (WLMT) (Sharma, 2003), respectively. Verbal *d'* from the CPT-IP was used as a sensitivity measure of discrimination of signal from the false alarms. The percentage of perseverative errors in the WCST indexed executive functions. Within the WLMT, trial-to-trial transfer measured verbal memory and learning.

### 2.2. Imaging

DTI data were acquired on a 3T Siemens Tim Trio whole-body scanner in 30 directions ($b = 1000$ s/mm$^2$) with 2 averages (slices = 48, thickness = 3.2 mm, TE = 90 ms, TR = 6300 ms, flip angle = 90°, matrix = 128 × 128, FOV = 240 mm). For each average, one b = 0 reference image was acquired.

The FA and RD maps were separately analyzed using FSL 4.1 (Smith et al., 2006). Diffusion scans were skull-stripped and manually checked for optimum brain extraction using the brain extraction tool (BET)(Hua et al., 2008). Eddy current and motion artefacts were corrected before all subjects' FA data were aligned into the MNI152 FA template using nonlinear registration. The diffusion tensors were fitted at each voxel on the corrected data. Voxelwise statistical analyses in these FA/RD maps were carried out using the Tract-Based Spatial Statistics (TBSS) applying 10,000 permutations. The mean FA image was created and thinned to generate a mean FA skeleton which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics. Threshold-free cluster enhancements (TFCE) were examined among the study groups correcting for multiple comparisons using the familywise error (FWE) correction at $p < 0.05$ within *Randomise* 4.1.9. The Johns Hopkins University (JHU) White Matter Tractography Atlas (Mori et al., 2008) was used to identify regions with FA/RD changes.

The FA/RD were extracted for each subject from the regions with significant diffusion changes within each contrast. Using the co-ordinates from the contrasts that showed diffusion changes, diffusion data were extracted from the contrasts that did not show changes within FSL for posthoc analyses. We conducted a group-wise comparison of primary diffusion direction (PDD) dispersion within these clusters to investigate complex fiber architecture (e.g. crossing fibers).

### 2.3. Statistical plan

Within FSL, three independent contrasts (HC/SZ, HC/FDR and FDR/SZ) examined FA/RD differences separately using ANCOVA models by including age and sex as covariates. FA/RD extracted from significant clusters were examined within forward stepwise linear regression models for the variance contributed by age, sex and FA/RD. FA/RD changes that remained significant after removing the effects of age and sex are reported. Using ANCOVA, we compared cognitive performances among the groups controlling for age and sex, and then correlated them with the FA/RD using partial correlations correcting for multiple testing. Only corrected *p*-values are reported.

## 3. Results

### 3.1. Demographic and clinical

Although the main effect of group on age was not significant ($p = 0.08$), FDR were younger compared to both schizophrenia ($p = 0.048$) and HC ($p = 0.043$). There were more females among FDR and HC compared to schizophrenia ($\chi^2 = 13.54$, df 2, $p = 0.001$). Hence, age and sex were covaried in all our analyses and variance contributed by age and sex for the FA/RD changes was estimated. Mean illness duration of patients was 3.35 ± 2.84 years (Table 1).

### 3.2. FSL analysis

#### 3.2.1. Diffusion measures

Schizophrenia subjects showed significant FA reductions compared to HC in the left SLF ($p = 0.022$), the right SLF ($p = 0.016$), forceps minor ($p = 0.04$), and the right uncinate fasciculus ($p = 0.04$) regions (Fig. 1). FA did not differ in the FDR and schizophrenia, and FDR and HC contrasts. No regions showed increased FA in any of the contrasts.

Schizophrenia subjects showed increased RD compared to HC in the forceps minor ($p = 0.0025$), the left ($p = 0.008$) and the right SLF ($p = 0.0055$) regions approximately within the same coordinates as FA was reduced. Like FA, RD did not differ in the FDR/schizophrenia and FDR/HC contrasts. No regions with decreased RD were detected.

#### 3.2.2. Extracted FA

*3.2.2.1. Schizophrenia Vs HC.* Forward stepwise regression models noted FA reduction in the forceps minor region, sex and left SLF region (in that