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Connectivity-enhanced diffusion analysis reveals white matter density disruptions in first episode and chronic schizophrenia

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ABSTRACT

Reduced fractional anisotropy (FA) is a well-established correlate of schizophrenia, but it remains unclear whether these tensor-based differences are the result of axon damage and/or organizational changes and whether the changes are progressive in the adult course of illness. Diffusion MRI data were collected in 81 schizophrenia patients (54 first episode and 27 chronic) and 64 controls. Analysis of FA was combined with "fixel-based" analysis, the latter of which leverages connectivity and crossing-fiber information to assess both fiber bundle density and organizational complexity (i.e., presence and magnitude of off-axis diffusion signal). Compared with controls, patients with schizophrenia displayed clusters of significantly lower FA in the bilateral frontal lobes, right dorsal centrum semiovale, and the left anterior limb of the internal capsule. All FA-based group differences overlapped substantially with regions containing complex fiber architecture. FA within these clusters was positively correlated with principal axis fiber density, but inversely correlated with both secondary/tertiary axis fiber density and voxel-wise fiber complexity. Crossing fiber complexity had the strongest (inverse) association with FA ($r = -0.82$). When crossing fiber structure was modeled in the MRtrix fixel-based analysis pipeline, patients exhibited significantly lower fiber density compared to controls in the dorsal and posterior corpus callosum (central, postcentral, and forceps major). Findings of lower FA in patients with schizophrenia likely reflect two inversely related signals: reduced density of principal axis fiber tracts and increased off-axis diffusion sources. Whereas the former confirms at least some regions where myelin and or/axon count are lower in schizophrenia, the latter indicates that the FA signal from principal axis fiber coherence is broadly contaminated by macrostructural complexity, and therefore does not necessarily reflect microstructural group differences. These results underline the need to move beyond tensor-based models in favor of acquisition and analysis techniques that can help disambiguate different sources of white matter disruptions associated with schizophrenia.

1. Introduction

Schizophrenia is widely viewed as a disorder of brain connectivity. However, the extent to which brain dysfunction in schizophrenia may be due to alterations in the structural connections between neuronal populations remains unclear. Fractional Anisotropy (FA) is a commonly used tensor-based measure from diffusion weighted imaging that reflects the relative amount of water diffusion along a principal axis within a voxel of brain tissue. Schizophrenia spectrum disorders are associated with decreased FA in many white matter tracts, in particular in the corpus callosum, as well as in fronto-thalamic, fronto-striatal, and fronto-temporal regions (Canu et al., 2014; Pettersson-Yeo et al., 2011). These findings are often interpreted as indicative of reduced myelination or tract "integrity." However, the interpretation of FA differences is problematic, particularly in brain regions containing crossing fibers (Jbabdi et al., 2010; Tournier et al., 2011). Evidence suggests that at least one third (and up to 90%) of white matter voxels contain crossing fibers, virtually invalidating the use of the tensor model on which FA is based as a tool for making inferences about microstructural properties of white matter in specific bundles (Behrens et al., 2007; Jeurissen et al., 2013).

Of the available techniques, constrained spherical deconvolution (CSD) is best able to detect voxels containing crossing fibers in simulated data (known ground truth) at b-values typical for clinical studies

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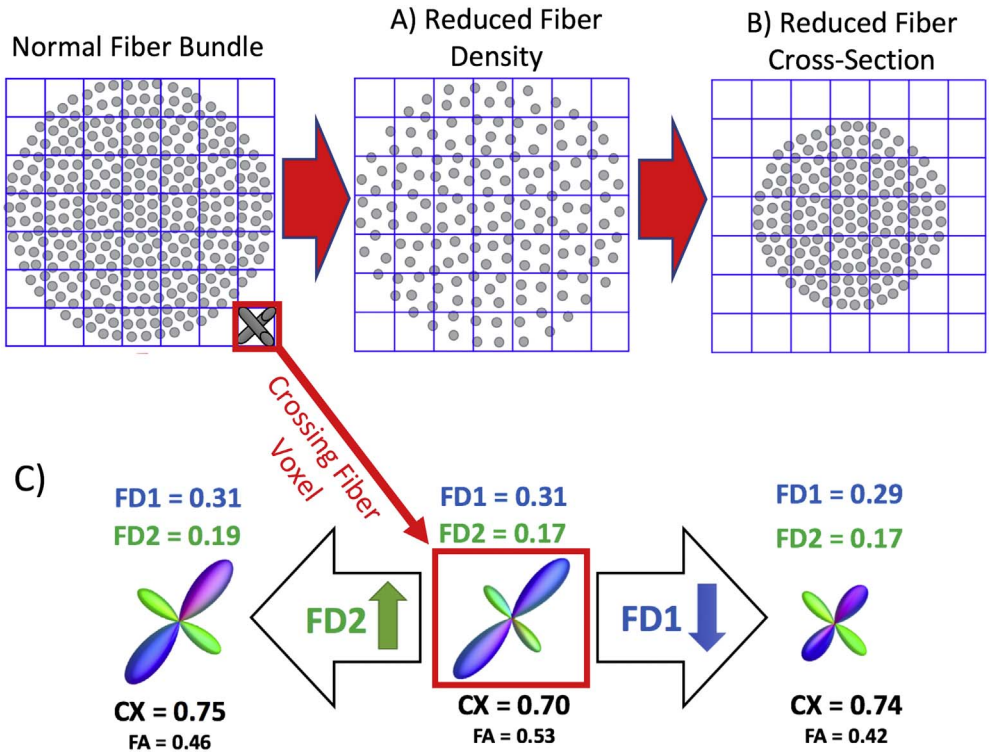

Fig. 1. Schematic of Fiber Density Reduction (A) and Fiber Cross-Section Reduction (B). (C) Example of how changes in the relative FD in a crossing fiber region affects complexity (CX). Complexity (CX) metrics will be higher if there is a relative increase in the FD2 (density of the second fiber population in a voxel) or if there is a decrease in the FD1 (density of the primary fiber population within a voxel). A and B adapted with permission from (Raffelt et al., 2016).

(e.g., b = 1000; Wilkins et al., 2015). MRtrix3's Fixel-based analysis pipeline uses constrained spherical deconvolution and underlying tractography to examine the properties of individual fiber populations within a voxel ("fixels") and can therefore go beyond whole-voxel FA estimation to provide more anatomically specific information about the micro and macrostructural properties of white matter populations, particularly in crossing fiber regions. While FA captures information about overall relative diffusion patterns in a voxel, studies in both phantom and human data show that fixel-based analysis can approximate both the density and macrostructural cross-section of distinct fiber bundles traversing a voxel (Raffelt et al., 2015, 2016). In addition, the fixel-based pipeline can provide a measure of the degree of organizational complexity of distinct fiber populations within a voxel (Fig. 1c; Riffert et al., 2014).

In the present study, we sought to examine schizophrenia-linked white matter changes using typical FA analysis and then to further investigate the sources of FA differences using fixel-based analysis. Based on the existing literature linking FA decreases to schizophrenia (Ellison-Wright and Bullmore, 2009; Samartzis et al., 2013) and on post-mortem studies that demonstrate structural oligodendrocyte alterations and axonal myelin damage in schizophrenia patients (Bernstein et al., 2015; Vikhreva et al., 2016), we hypothesized that schizophrenia patients would exhibit lower FA in frontal and callosal white matter and that these FA differences would be attributable to reductions in principal axis fiber density. In addition, since it is possible that more off-axis diffusion signal in or near crossing pathways could also contribute to lower FA, we performed exploratory whole brain analyses to test the hypothesis that crossing fiber complexity is higher in patients compared to controls.

2. Methods and materials

2.1. Sample recruitment and demographics

All participants were recruited as part of the Center for Neurocognition and Emotion in Schizophrenia research. The study protocol and consent form were approved by the institutional review boards of the University of California, Los Angeles (UCLA) and Yale University, and all participants provided written informed consent. The present sample included individuals who had recently experienced their first episode (FE) of schizophrenia (within two years prior to recruitment), individuals with chronic schizophrenia, and matched healthy controls. Schizophrenia diagnosis was determined using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First et al., 1995). Patients were excluded on the basis of drug induced psychosis, substance dependence within the last 6 months, or history of traumatic brain injury or neurological disorder. Patients were recruited from public and private clinics and hospitals in the Los Angeles area, and all FE patients were under the care of the UCLA Aftercare Research Program. All FE patients were clinically stabilized at the time of test (61% Risperidone, 19% Olanzapine, 6% Aripiprazole, 8% Other antipsychotic, 6% missing; missing data were due to computer error). Chronic patients were drawn from a sample of patients previously recruited and treated as FE patients through the Aftercare program, but whose initial psychotic episode occurred 5 years or more prior to the imaging assessment. The medication profile of the Chronic patient subset was somewhat more diverse: 33% Risperidone, 20% Aripiprazole, 11% Haldol, 30% other antipsychotic, 6% no current antipsychotic medication.

Healthy control participants were recruited through local advertisements (newspapers and posters). Control participants were excluded based on the following criteria: history of any major DSM-IV Axis I disorder, neurological disorder, traumatic brain injury, or drug dependence or recent abuse (as assessed by the SCID-I). Potential control participants were also excluded if they had a first-degree relative with psychosis, or if they were currently pregnant.

The initial MRI sample comprised 163 patients and controls aged 18–40. Following visual inspection for scan quality, 18 scans were removed: 15 based on Field of View errors (7 controls) and 3 based on overt MR artifacts, such as blurring or warping (2 controls). The final sample included 81 patients (54 FE and 27 Chronic) and 64 age-matched controls. Patients and controls did not differ significantly in age ($t(139) = 1.56$, $p = 0.12$) or sex ($X^2 = 0.39$, $p = 0.53$). Sample demographics are presented in Table 1.