

## Altered White Matter Myelination in Chronic Schizophrenia

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### Introduction

Altered white matter microstructure in schizophrenia has been suggested by both histological data and imaging studies based on Diffusion Tensor Imaging (DTI) approach (1). The DTI literature widely reports reduced fractional anisotropy (FA), a DTI-based measure of microstructural integrity. However, the underlying pathophysiology remains unclear as differences in FA can stem from a variety of causes including differences in myelination and fiber density and geometry. The goal of this study was to investigate axonal density and myelination in schizophrenia using a recently proposed two-compartment diffusion model of white matter (2) and Diffusion Kurtosis Imaging (DKI).

### Methods

Seventeen right handed male patients, with a diagnosis of chronic schizophrenia and eighteen male healthy control (HC) participants with ages between 30 and 55 years old participated in the study. The Structured Clinical Interview for DSM-IV (SCID) was used to confirm that subjects in the patient group met the criteria for a diagnosis of schizophrenia. The Non-Patient edition (SCID-I/NP) was used to screen the control subjects for Axis I disorders. All attempts were made to match the two groups on age and parental socio-economic status (SES) by selecting control subjects with similar values for these variables. Thus, there were no significant differences between groups in age and parental SES. There were also no significant differences between groups in handedness.

DKI was used in conjunction with a newly proposed two-compartment model of white matter, which provides metrics that differentially describes intra- and extra-axonal white matter compartments (2). These metrics include the axonal water fraction (*AWF*), a measure of axonal density, the tortuosity of the extra-axonal space (*Ex-Tort*), an indirect measure of myelination, and compartment specific diffusivity measures such as intra-axonal and extra-axonal diffusivities (*InD* and *ExD*) and their axial (*AD*) and radial (*RD*) components. Three-dimensional parametric maps of the measures of interest were created for each subject (similar to 2, 3) and between group differences were examined using Tract-Based Spatial Statistic (TBSS) implemented within the FSL software package.

Imaging data was obtained using a 3T Trio MRI Scanner (Siemens Medical Solutions, Erlangen, Germany). Images were acquired using a body coil for transmission and a 12-element coil for reception. Approximate full brain coverage was obtained by acquiring 55 contiguous slices with a slice thickness of 2.3 mm (voxel size=2.3x2.3x2.3 mm<sup>2</sup>). Other imaging parameters included TR = 8000ms, TE = 97ms and a field of view of 230 x 230 mm<sup>2</sup>, and parallel imaging with an acceleration factor of 2. Diffusion weighted data was acquired for a total of 64 uniformly distributed gradient directions and for two *b* values (*b* = 1000 s/mm<sup>2</sup> and *b*=2000 s/mm<sup>2</sup>). Additionally, nine sets of images with *b*=0 s/mm<sup>2</sup> were also obtained. The total imaging time was around 17 minutes. All images were corrected for motion and distortions from B0-field inhomogeneities.

### Results

Significantly decreased *Ex-Tort* was found in the schizophrenia group in extended white matter regions, which include the corpus callosum, corona radiata, internal capsule, superior longitudinal fasciculus, and optic and auditory radiations (Figure 1). *Ex-TORT* differences between groups were strongly associated with FA differences, which were observed in similar regions. No significant differences between groups were found in the *AWF* and other intra-axonal diffusion metrics.

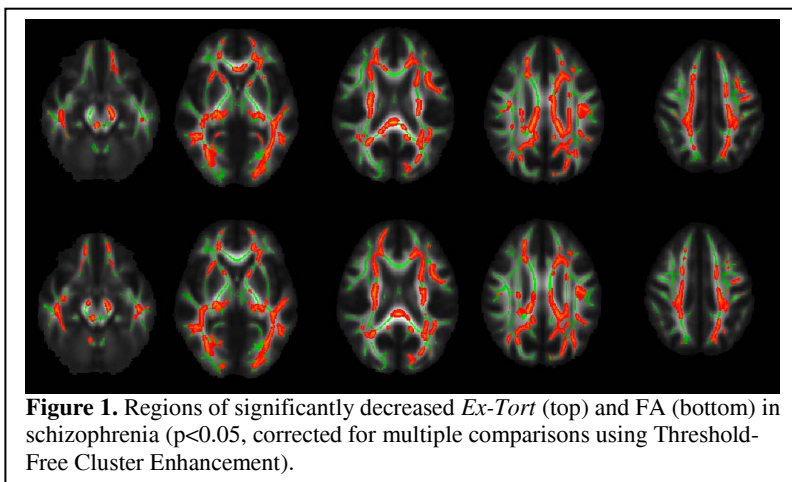
### Discussion

This is the first study, to our knowledge, to examine myelination and axonal density properties in schizophrenia using a two-compartment model of intra and extra-axonal white matter and DKI. Our results suggest that FA differences in chronic schizophrenia primarily stem from myelination deficits and are consistent with previous reports of altered gene polymorphisms and gene expression in schizophrenia for myelin and oligodendrocytes related genes (4). Thus, our data provide additional evidence in support of the dysmyelination hypothesis in schizophrenia. This evidence can be instrumental in designing and potentially monitoring future targeted treatment approaches given that white matter has been proposed as a potential new target for development of new treatments (4) such as agents that directly target oligodendrocytes.

### Conclusions

Atypical myelination appears to be a pervasive pathophysiological feature in chronic schizophrenia. Fiber density does not appear to be significantly affected in this population. These findings have direct implications for implementing and potentially monitoring treatment approaches.

**References:** 1. Shenton et al., *Dialogues Clin Neurosci*, 12, p. 317, 2010; 2. Fieremans et al., *Neuroimage* 58, p. 177, 2011; 3. Jensen and Helpert, *NMR Biomed* 23, p. 659, 2010; 4. Walterfang, *Expert Rev Neurother* 11, p. 971, 2011.



**Figure 1.** Regions of significantly decreased *Ex-Tort* (top) and FA (bottom) in schizophrenia ( $p < 0.05$ , corrected for multiple comparisons using Threshold-Free Cluster Enhancement).