Tract-Specific Anisotropy Measures and Temporal Characteristics of Schizophrenia Abnormalities

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Diffusion tensor imaging (DTI) [1] is commonly used to examine white matter microstructure in neuropsychiatric conditions such as schizophrenia. New image processing algorithms hold the promise to increase the accuracy and sensitivity of DTI quantification. Here we implemented a fiber tracking algorithm and used it to investigate the temporal nature of white matter abnormalities in schizophrenia.

Methods: Seventy-six chronic and thirty-nine first-episode patients with schizophrenia and one-hundred-sixteen healthy volunteers underwent psychological assessment and DTI. The diagnosis of schizophrenia was confirmed by a structured diagnostic interview (Comprehensive Assessment of Psychiatric Symptoms and History; CASH). Drug testing and medical screening was performed to exclude patients with substance abuse and cardiovascular disease that might affect MRI results. DTI were acquired using a pulsed-gradient spin-echo sequence with EPI-acquisition (TR=4100ms, TE=80ms, FOV=21cm, matrix =128x128, 32 slices, thickness=3mm skip 1mm, b-factor=1250 s/mm^2, 12 gradient directions, 5 averages). Quantitative DTI tractography based on a streamline/brute-force algorithm [2] was used to quantify the fractional anisotropy (FA) of the forceps minor and the pyramidal tracts bilaterally. Target regions for tractography were defined in MNI space using an average of all healthy subjects' SPM2 (Wellcome Department of Cognitive Neurology, London) normalized FA images from the DTI.

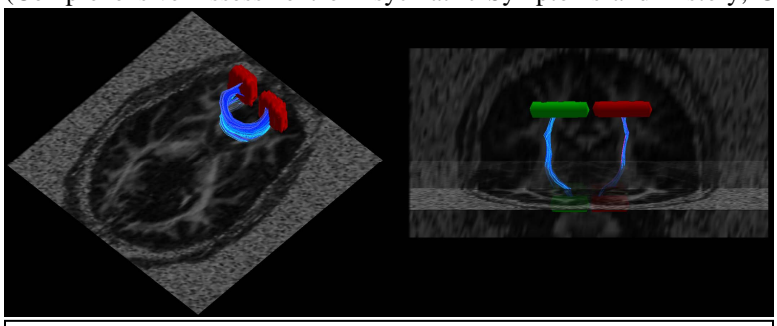

Figure 1: Multi-ROI brute-force fiber tracking of (A) the forceps minor and (B) the bilateral pyramidal tracts.

Results: A total of 231 subjects were scanned and 13 scans were removed because of poor image quality that was likely due to motion (8 patients, and 5 healthy controls). The remaining DTI data were used to track the forceps minor and pyramidal white matter tracts using a brute force streamline tractography algorithm (Figure 1). In healthy controls, age and FA of each tract showed a negative correlation. FA measures were adjusted based on the healthy age related decline so that reported values represent the residuals from the age versus FA regression lines generated from the healthy subjects. Age adjusted FA values of the forceps minor were non-significantly lower in first-break patients with schizophrenia ($p = 0.08$) and further decreased in chronic patients with schizophrenia ($p < 0.001$) when compared to healthy control subjects (Figure 2). No significant group differences were observed in the pyramidal tracts. Figure 3 shows an FA decline in the forceps minor of patients that is related to illness duration after correcting for normal aging effects on FA ($r = -0.33$, slope = 0.0092 FA units/decade, $p < 0.001$).

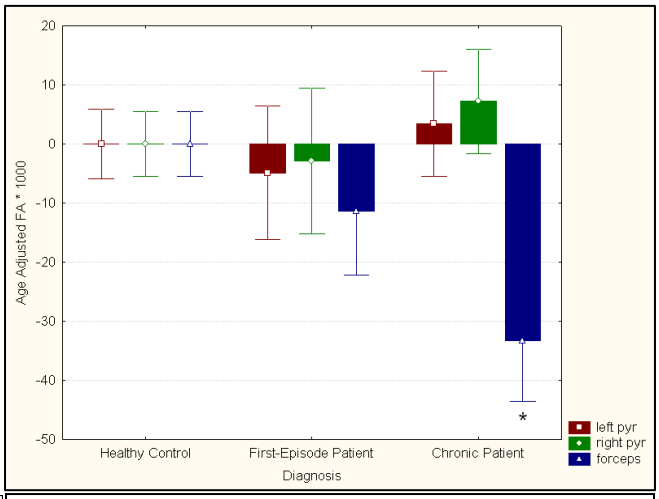

Figure 2: Group differences in age corrected FA values. Mean FA from quantitative DTI tractography.

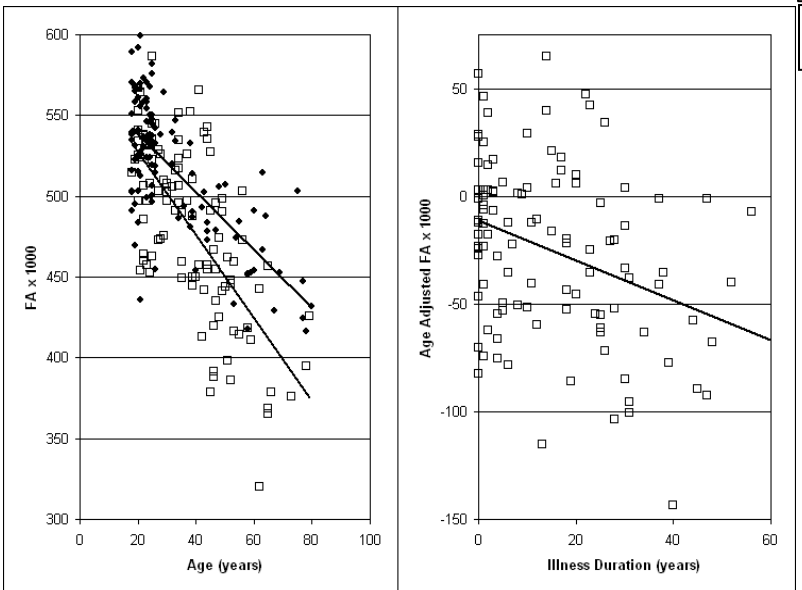

Figure 3: The forceps minor FA of ill patients (open squares) was age corrected using the slope of the healthy subjects (left, black dots) and the residuals are plotted with the duration of illness (right).

Conclusion: The quantitative DTI tractography approach revealed a significant decline in FA that was correlated with the duration of illness in the forceps minor. This FA decline in patients is beyond that correlated with healthy aging. The findings suggest that there are white matter tract-specific degenerative mechanisms that may be present at the point of illness onset and that progress throughout the illness. This warrants the investigation into therapeutic means to arrest or slow down such pathway-specific FA decline early in the disease.

1. Basser, P.J., et al., Biophys J, 1994. **66**(1): p. 259-67.
2. Huang, H., et al., Magn Reson Med, 2004. **52**(3): p. 559-65.

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