

# Widespread decrease of fractional anisotropy in never treated schizophrenia patients with disease duration over 5 years

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**Purpose:**

Though many previous studies provided evidences to support the regional or global decrease of fractional anisotropy (FA) in schizophrenia, the results were quite inconsistent. Most of them included the chronic and medicated patients, and thus results may be a combination of disease itself, disease duration as well as antipsychotic-medication. Furthermore, some report revealed that the deficits only significant in the chronic patients rather than first episode schizophrenia<sup>1</sup>, indicating that antipsychotic-medication and/or disease duration are involved in the development of white matter abnormality. The rare case of chronic but never-treated patients from western China provided a unique opportunity to study effect of chronic disease duration on the white matter. Since the disease duration and age are highly correlated, studying age effect on white matter is more applicable. Thus, the aim of current study was to explore the white matter alterations in never-treated, chronic schizophrenia patients as well as the age effect on the white matter microstructure.

**Methods:**

This study was approved by the local ethical committee and written informed consent was obtained from all subjects. 26 never-treated, chronic schizophrenia patients with disease duration ranged from 5 to 47 years and 28 healthy comparison subjects were recruited in the present research. Both patients and healthy controls were performed MR examination via a 3-Tesla GE MRI system with an 8 channel phase array head coil to acquire DTI data. DTI preprocessing was performed using FSL software (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl>). Eddy currents related distortions were corrected and all the images aligned to the mean reference volume. FA images were calculated and then non-linearly registered into Montreal Neurological Institute (MNI) standard space. Then, the mean FA image (threshold of 0.2) was created and thinned to create 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 were fed into voxel-wise cross-subject statistics. Mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were conducted in the same way and aligned to the FA skeleton. A voxel-wise statistical analysis was applied to investigate differences between the patient group and the healthy control group. Statistical significance was set at  $p < 0.05$  with threshold-free cluster enhancement (TFCE) correction for multiple comparisons. Positive and Negative Syndrome Scale (PANSS) were used to assess the clinical symptoms of schizophrenia patients. Besides, correlation analysis between significant difference of FA in patient group and scale scores was performed to reveal the potential association between the anatomical connectivity deficits and clinical symptoms. Furthermore, linear regression analysis was used to explore the potential association between age and white matter microstructure.

**Results:**

Compared to the control group, schizophrenia patients showed significantly decreased FA of white matter throughout the brain, including the bilateral anterior thalamic radiations, corticospinal tracts, cingulum (cingulate gyrus), forceps minor, forceps major, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculus ( $P < 0.05$ , Figure 1). Meanwhile, the patients also showed increased MD, AD and RD in the similar areas. The FA of forceps minor, right superior longitudinal fasciculus, and bilateral corticospinal tracts was negatively correlated with the severities of symptoms in patients as identified by PANSS scores for total score, thought disturbance, activation, depression or impulsive aggression (Table 1). Furthermore, linear regression analysis exhibited accelerated decrease of FA in forceps minor than controls ( $P < 0.05$ , Figure 2).

**Discussion:**

The current study included a rare case of chronic but never-treated schizophrenia patients and exhibited significantly widespread decrease of FA, especially in anterior thalamic radiation, corticospinal tract, cingulum (cingulate gyrus), forceps minor, inferior fronto-occipital fasciculus and superior longitudinal fasciculus. However, only FA in forceps minor showed accelerated decrease of FA than controls. The decrease of FA in forceps minor may be resulted from neuroprogressive mechanism<sup>2</sup> characterized by accelerated cerebral deficits in schizophrenia beyond the normal aging. These obvious alterations of white matter microstructure at the relatively latter stage of disease may in some degree facilitate to partly explain the complex neuropathological mechanism of schizophrenia. In addition, a strong link between symptoms and FA displayed a consensus between white matter microstructure and clinical manifestations.

**Conclusion:**

The current study revealed widespread damage of white matter microstructure at the latter phase of schizophrenia without the confounding effect of medication, especially in anterior thalamic radiation, corticospinal tract, cingulum (cingulate gyrus), forceps minor, inferior fronto-occipital fasciculus and superior longitudinal fasciculus. However, only forceps minor exhibited faster aging effect than controls suggesting the critical role of forceps minor in the progressive mechanism of schizophrenia.

**References:**

1. White, T., et al., Schizophr. Bull. 2013. 39 (5), 1077–1086.  
2. Kraepelin E. Dementia praecox and paraphrenia. 1971.

**Figure 1.** Results of TBSS analysis between patients and control. Green voxels: TBSS skeleton. Red-yellow voxels: voxels with patients FA < healthy FA (A); voxels with patients MD > healthy MD (B); voxels with patients AD > healthy AD (C); voxels with patients RD > healthy RD (D) (TFCE multiple comparisons correction ( $p = 0.05$ ), statistical significance is higher where the color assigned to the voxel is brighter)

**Figure 2.** Linear regression between age and FA. Patients showed accelerated decrease of FA in forceps minor than controls.

**Table 1.** Correlation analyses between scores of clinical symptoms and FA  
\* Correlation is significant at the 0.05 level (2-tailed).  
Total: PANSS total scores; TD: Thought disturbance, Act: Activation; Dep: Depression; Impul: Impulsive aggression; CST: Corticospinal tract; FM: Forceps minor; SLF: Superior longitudinal fasciculus

