White matter microstructural disruptions in drug-naïve patients with first-episode schizophrenia: a diffusion tensor imaging study

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Aims and objectives

Schizophrenia is proposed as a multifactorial and complex disorder [1]. Among the factors involved in its pathogenesis, the disruptions in the connectivity between brain regions was hypothesized as the core feature underlying the outbreak of schizophrenia[2]. In according with the hypothesis of disturbance of brain network in schizophrenia, convergent evidence from neuropathological, functional and structural imaging are increasing in recent years.[3]

Diffusion tensor imaging (DTI) is a novel MRI technique that provides a window to detect information about white matter integrity and organization based on Brownian motion of water molecule[4]. In DTI indices, the two most commonly used is Mean diffusivity(MD) and Fractional anisotropy (FA)[5].

Tract-based spatial statistics (TBSS), a new introduced automated DTI data analysis algorithm [6], which project all subjects DTI parameter to a group average "fiber skeleton", reduces potentials for misregistration, and is considered to be more suitable for voxel-wise brain analysis.

To determine whether DTI abnormalities are present in the early stages of schizophrenia, we conducted TBSS analysis on DTI data in whole brain pattern in first episode neuroleptics-naive schizophrenia patients compared to healthy control.
Methods and materials

2.1 Participants

36 FES patients (21females/15males) and 41 health controls (21females/20 males) were recruited in this study under the Institute of Mental Health, Peking University, China. The diagnosis of FES was based on the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Patients referred to the program should meet the following criteria: 1) age 15-45 years, 2) experiencing their first episode of schizophrenia, 3) no prior treatment with antipsychotic medication, 4) not complicated by other psychiatric disorders. Healthy subjects were matched to the patients by age, sex, handness- and years of education.

2.2 Imaging acquisition

We used GE Signa HDx 3.0T MRI system equipped with an 8-channel brain phased array coil to acquire diffusion tensor images. DTI was performed along 25 non-collinear directions with the single-shot echo-planar imaging (EPI) and parallel technique. The protocol parameter in detail are as follows: acquisition matrix = 128 × 128, TE = Minimum, TR = 16000 ms, #eld of view =240 mm×240 mm, slice Thickness =2.5 mm, Gap =0 Mm. b Value of 1000 was chosen based on previous studies.

2.3 Data processing

All DTI data was processed in the FSL 4.1.9 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl). Statistical analysis in demographic variables were performed using the SPSS 17.0 for Windows program (SPSS Inc., Chicago, IL, USA). The differences between the patients with schizophrenia and the healthy controls in age, education and gender were tested with independent sample t-tests and Chi-square test respectively. The statistical threshold is traditionally set at P<0.05.

Comparison of anisotropy differences between groups were performed with permutation-based analysis, using 5000 random permutations. The statistical threshold was also set at P < 0.05.
Results

No significant difference was found in age, gender, education level, and handedness between the patient group and the control group. Patients with first episode schizophrenia exhibited three cluster of significant FA reductions compared with health controls in voxelwise analysis (cluster size: 1165). Cluster A included SLE, CS, PCC, ATR; cluster B included SLE, ATR; cluster C included SLE. In cluster A, mean FA values in patients and control subjects were 0.522 (SD=0.063) and 0.580 (SD=0.063), respectively; in cluster B they were 0.552 (SD=0.052) and 0.592 (SD=0.042), respectively; in cluster C, they were 0.514 (SD=0.029) and 0.549 (SD=0.035), respectively. There were no significant group difference in the voxelwise analysis with regard to MD. Also, no significant association were found between reduced FA and age (p=0.320, p=0.765, p=0.795 for cluster A, cluster B, cluster C, respectively) in patient group.
Fig. 1: Results are overlaid on the axial sections of the T1WI template. Blue-green voxels represent cluster A regions, violet voxels represent cluster B regions, red-yellow voxels represent cluster C regions.

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Fig. 2: Results are overlaid on the coronal sections of the T1WI template. Blue-green voxels represent cluster A regions, violet voxels represent cluster B regions, red-yellow voxels represent cluster C regions.

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Fig. 3: Results are overlaid on the sagittal sections of the T1WI template. Blue-green voxels represent cluster A regions, violet voxels represent cluster B regions, red-yellow voxels represent cluster C regions.

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Conclusion

In the present study, patients with FE schizophrenia showed a statistically significant decrease in FA in cortico-subcortical pathways (CST) in the left hemisphere, association fiber (SLE) and limb system (CB) in the bilateral hemisphere compared with healthy controls. In addition, there were no significant differences between patients with schizophrenia and healthy controls with regard to MD.

In analysis of FA, regional FA reductions in FE schizophrenia were found in the bilateral SLF#CB and right CST, which are in line with the majority of previous reports [7]. FA reductions in CST were less reported in previous publications compared with SLF and CB, there were some characteristics in the lesions of CST. Douaud G, et al reported structural deficits revealed in adolescent-onset schizophrenia patients in the CST were less marked or even disappeared in the follow-up study of 2.5 years [8]. In several other studies revealing positive findings in CST, adolescent patients were also recruited as the samples of study [8, 9, 10], differing from studies about chronic patients which rarely reported abnormalities in CST. Our results showed FA values in CST in schizophrenia patients were significantly lower than these in healthy controls, we speculate that it is due to the fact patients' age were relative young (21.83±4.17) in current study.

Several pathophysiological processes were used to explain the mechanism underlying FA alterations in schizophrenia. FA value is calculated through a ellipsoid tensor model within a single voxel [4]. Each voxel comprise several kinds of membranous components, including cell membrane, organelle membrane and myelin, and alterations in any of those may change FA values. In addition, the spatial distributions of axonal also have an impact on FA alterations. Among those factors influencing FA values, axonal membranes are considered the principal determinants of anisotropy in WM.

This present study failed to detect significant difference in MD between groups and lacked association between age and FA values in 3 clusters in patient group. The negative finding of MD combining FA reduction in patients might suggest that white matter experienced fiber branches "pruning" rather than demyelination in affected tracts [11].

Conclusion

Having excluded the potential effects of confounds like medication exposure and co-morbidities in chronic schizophrenia, the current data show that WM changes in patients with schizophrenia present at their first break, which support the hypothesis of dis-connectivity in schizophrenia and lends evidence to the conception of disturbed neurodevelopment in schizophrenia. A new treatment strategy might be developed by maintaining and restoring the integrity of WM.
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