Research report

Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: A diffusion tensor study using TBSS

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HIGHLIGHTS

- Collected patients which had never been exposed to antipsychotic treatment.
- Examined FA, MD, AD and RD can apply more information underlying the disease.
- The relationships between white matter integrity and cognitive function.
- FA value may be more sensitive than other DTI indices in the schizophrenia.
- Disruption of white matter integrity may contribute to cognitive deficits.

ARTICLE INFO

ABSTRACT

Background: Disrupted white matter (WM) integrity is the pathological hallmark of schizophrenia. Previous studies have reported the cognitive deficits that are associated with WM disruption in schizophrenia with anti-psychiatric treatment. However, no study has yet revealed the correlation between cognition and WM abnormalities in never-medicated chronic schizophrenia.

Methods: We used the diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS) approach to investigate the whole-brain difference in the WM fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) values between 17 schizophrenia patients and 17 healthy controls matched in age, gender and education level. Patients' cognition was assessed through the MATRICS Consensus Cognitive Battery (MCCB). We explored the association between WM reduction and cognitive, clinical characteristics (severity of clinical symptoms, age, age of onset, illness duration).

Results: Voxel-wise statistics revealed that schizophrenia patients showed significant FA reduction in left inferior longitudinal fasciculus (ILF) and left inferior fronto-occipital fasciculus (IFOF), and no difference in MD, AD and RD as compared to healthy subjects. Furthermore, in the patients group, lower FA value of the left ILF and left IFOF significantly correlated with worse processing speed, as well as verbal learning and visual learning abilities. There was no correlation between the FA value and the severity of clinical symptoms, age, and age of onset or illness duration.

Conclusion: Our results provide evidence to support that the disconnection of WM pathways may contribute to the pathophysiology of schizophrenia and suggest that the disturbance of left ILF and left IFOF integrity may contribute to cognitive deficits in schizophrenia, independent of effects of antipsychotic medication.

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1. Introduction

Schizophrenia is a common and severe disabling mental disease with disturbances of social, behavioral and cognitive functions.

The disconnection within and between brain regions may be considered as a core underlying pathophysiological mechanism in schizophrenia [1]. The growing evidence has suggested that the alterations in white matter (WM) may be the core basis for this disconnection [2,3]. Evidences from neuropathology and neuroimaging have pointed to reduction in oligodendrocyte numbers, abnormalities microstructure of myelin sheaths and/or axon, or disordered neuronal architecture, which are the causes of WM pathology in schizophrenia [2–5]. WM fiber tracts form the basis

of the high-speed communication between brain regions, and the alterations of the WM pathways could explain the clinical and cognitive symptoms associated with the disease. Abnormalities in the structural integrity of WM are present in patients with schizophrenia, particularly in frontal and temporal regions [6]. Negative symptoms in schizophrenia have been connected to the disrupted integrity of corpus callosum [7]. Positive symptoms have been positively correlated with fiber tract integrity in left fronto-occipital fasciculus and left inferior longitudinal fasciculus [8]. Poor verbal working memory performance correlated with reduced integrity of superior longitudinal fasciculus [9]. Reductions in WM integrity in the frontal and temporal connections are associated with deficits in executive and motor function [10]. These findings may support the disconnection hypothesis in schizophrenia.

Diffusion tensor imaging (DTI) (as a non-invasive technique) has been widely used in vivo to investigate the information of WM based on water molecules diffusion [11–13]. Fractional anisotropy (FA) and mean diffusivity (MD) are the most two commonly used measures of WM integrity in the living brain. FA describes the degree of anisotropy of water molecules diffusion that refers to the fibers structural integrity, degree of myelination, fiber tracts coherence and fiber diameter and packing density in WM [14–16]. Any of these factors or a combination of them could impact FA. The FA value is from 0 to 1, of which 0 reflects isotropic diffusion and 1 reflects anisotropic diffusion [17]. The decrease in FA implies damage of myelin or axons and/or loss coherence [4]. Another important index derived from DTI is MD, a quantitative measure of directionally average diffusion and independent of fiber directionality, which reflects compactness and intercellular space [14]. The increase in MD implies enlargement in the extracellular space and raised water diffusivity in these regions due to the loss of axons or myelination [18]. In addition to FA and MD, axial diffusivity (AD) and radial diffusivity (RD) are two other indices derived from DTI, which are more specific to underlying pathologies of axon and myelin. AD corresponds to diffusion in the primary directions, while RD corresponds to the average diffusion in the perpendicular directions. In animal experiments, reduced AD reflects axonal damage, while increased RD reflects myelin damage respectively [19,20]. Over the past few decades, an increasing number of DTI studies have been widely used to investigate the WM alterations in schizophrenia [12,21]. Previous studies reported significant changes of DTI measures in various brain regions of schizophrenia [22–25].

As WM abnormalities are multi-regional, to fully investigate such connectivity, exploration of such abnormalities in the whole brain is necessary. The majority of prior DTI studies in schizophrenia can be limited by using region of interest (ROI) and voxel-based morphometry (VBM) to process DTI data. ROI requires manual placement of regions of interest, which can introduce bias and time consuming. VBM, as a fully automated structural MRI analysis method, has been used in many structural imaging techniques at the whole brain level without any specific hypotheses [26]. Although considerable findings have been reported and provided useful information for schizophrenia research, the method has its pitfalls. Alignment inaccuracies of WM fiber tracts between subjects can lead to a FA difference in the same tract [27]. Arbitrary choice of smoothness extent is another problem with VBM analysis. Smoothness increases the partial volume problem and affects the final result of FA [28]. A recent study showed that VBM is not an optimal method to analysis WM in schizophrenia [29]. Tract-based spatial statistics (TBSS) is a new approach which is also fully automated to investigate the whole brain without prespecification of tracts of interest [30]. Followed by projection onto an alignment-invariant tract representation (mean FA skeleton), TBSS solves the alignment and smoothing issues. This method has been applied to evaluate WM changes of schizophrenia [31–33].

To date, there have been a large number of DTI studies in schizophrenia, but the findings have yielded inconsistent results. Several factors, such as patients' characteristics, sample size, antipsychotic drugs, MR technique and DTI data post-processing methods, are responsible for the inconsistencies between the studies. Moreover, most of previous DTI studies have only examined patients on medication. This may impact the results since antipsychotic medication has been suggested to affect WM microstructure and brain anatomy [34–36]. One way to exclude potentially confounding effects is to compare never-medicated schizophrenia patients to healthy controls by using sensitivity and objectivity analysis methods. So far there are only a few DTI studies investigating the WM integrity in never-medicated schizophrenia patients [8,37–40]. These studies used ROI or VBM with the exception of one study. In addition, they did not detect the relationship between WM integrity and cognitive function.

In this study, to further understand the WM alterations underlying in schizophrenia, we used TBSS approach to evaluate diffusion indices (including FA, MD, AD and RD) in never-medicated chronic schizophrenia. Additionally, we examined the associations between WM disconnectivity and clinical symptoms as well as cognitive performance. To our knowledge, this is the first DTI study performed in never-medicated chronic schizophrenia. Therefore, we focused on patients with chronic schizophrenia, since a number of studies have shown that abnormalities FA may not present at illness onset [41–44]. Based on the above literature, we hypothesized that: (i) WM disconnection would be present in never-medicated chronic schizophrenia as compared with healthy controls; (ii) the changes of DTI indices would be partly related to the clinical symptoms and/or impaired cognitive performance.

2. Materials and methods

2.1. Subjects

Our subjects were 17 patients with schizophrenia (7 males and 10 females) and 17 healthy controls (6 males and 11 females). All subjects were right handed. Seventeen patients with chronic schizophrenia recruited from four counties (Gaobeidian, Xushui, Tangxian, and Gaoyang) in Hebei province in North China between March, 2011 and April, 2012, under the institute of Mental Health, Peking University, China. All the patients fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV. None of the patients had undergone previous antipsychotic treatment. The main reasons why patients did not receive any antipsychotic treatment were as follows: (1) lack of medical care in poor areas. (2) neglect the disease due to low education levels of patients and family members. The mean duration of illness was 15.41 ± 6.33 years. The severity of clinical symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS) at the time of scanning [45]. Seventeen healthy controls matched for age, sex and handedness were recruited from the community of Hebei province through advertisements. Exclusion criteria for healthy controls included having a family history of a psychiatric disorder and a first-degree relative with psychosis. Exclusion criteria for all subjects included a history of head injury, organic mental disorder, neurological disorder, serious medical or surgical illness and substance abuse. All subjects gave full written informed consent before participating in this study, which was approved by the University's Ethics Committee.

2.2. Cognition assessments

The MATRICS Consensus Cognitive Battery (MCCB) was used to assess the cognitive levels of all participants. The MCCB is a standardized battery for examining cognitive function for adults with schizophrenia [46,47]. The MCCB measures seven cognitive domains including processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving as well as social cognition [48]. Cognitive function examined in our study included: (1) Brief Assessment of Cognition in Schizophrenia (BACS), Category Fluency and Trail Making Test part A to measure processing speed; (2) Continuous Performance Test-Identical Pairs (CPT-IP) to measure attention/vigilance; (3) Wechsler Memory Scale (spatial and letter-number span) and Letter-Number Span to assess working memory; (4) Hopkins Verbal Learning Test to measure verbal learning; (5) Brief Visuospatial Memory Test to measure visual learning; (6) Neuropsychological Assessment Battery (NAB) to measure reasoning and problem solving; (7) Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) to measure social cognition. Patients' scores of seven cognitive domains were calculated from several sub-test scores by the Chinese norm