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ORIGINAL ARTICLE

Fronto-temporal connectivity in never-medicated patients with first-episode schizophrenia: A DTI study

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KEYWORDS

First episode schizophrenia;
DTI;
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Superior longitudinal fasciculus;
External capsule

Abstract *Purpose:* To assess fronto-temporal connectivity in never-medicated patients with first episode schizophrenia (FES).
Material and methods: Twelve never-medicated patients (median age = 25.5 y) with first episode schizophrenia (according to DSM-IV system) and sixteen demographically matched controls were enrolled in the study. Conventional MRI sequences were obtained. Single shot echo-planar DTI was acquired in 32 non-collinear directions. Tractography of the direct pathway of the superior longitudinal fasciculus (SLFd) and uncinate fasciculus of both hemispheres was performed, and ROIs at the anterior cingulum and external capsule of both hemispheres were drawn. Fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD) and Trace of the ROIs and reconstructed tracts were calculated. Group comparison was performed using independent sample *t*-test and Fisher's exact test.
Results: Compared to healthy participants, there was significant reduction of FA of the left external capsule ($p = 0.001$) with increase in RD and Trace ($p = .004, .048$ respectively). However, the right SLFd showed significant reduction of AD ($p = 0.005$) and the left SLFd showed significant reduction of its volume ($p = 0.02$).
Conclusion: In patients with FES, impaired white matter connectivity was recognized in the right SLFd and left external capsule associated with reduction in the volume of the left SLFd.

Abbreviations: AD, axial diffusivity; FA, fractional anisotropy; FES, first episode schizophrenia; RD, radial diffusivity; ROI, region of interest; SLF, superior longitudinal fasciculus; SLFd, the direct pathway of the superior longitudinal fasciculus

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1. Introduction

Schizophrenia is a serious and disabling neuropsychiatric illness characterized by cognitive dysfunction, hallucination and delusion with devastating consequences on the psychological and financial resources of the patients and community (1). The definite etiology of schizophrenia is not known. However, in 1906 Wernicke proposed that a disruption of fronto-temporal connectivity may partly explain some of the primary symptoms of schizophrenia (2). Since then, there has been growing evidence suggesting that abnormal brain connectivity may be the cardinal abnormality in schizophrenia (3).

Compared to conventional MRI, diffusion tensor imaging is a newly developed MRI technique that facilitates in vivo analysis of white matter fiber tracts in the brain. There are three methods used for quantitative analysis of DTI data: Voxel-based analysis, Tractography and ROI-based approach (4). Quantification by Fractional anisotropy (FA) is used as an indicator of fiber integrity (5). Several reports that included patients with chronic schizophrenia found FA reduction of the left uncinate fasciculus and superior longitudinal fasciculus (6–9) which represent major white matter tracts connecting the frontal and temporal lobes. Also fractional anisotropy reduction was documented in the right external capsule and right anterior cingulum (10,11). Other reports found no significant differences in FA between patients and healthy participants (12,13).

Compared to studies with chronic schizophrenia, there are few reports that investigate white matter integrity in patients with first-episode schizophrenia (14–18). Moreover, there are paucity of reports that investigate white matter integrity in never medicated patients and their results are inconsistent and inconclusive (19–22), probably as a result of clinical heterogeneity of the studied patients or different DTI approaches and methods of analysis. In addition, few reports have assessed other diffusivity indices (axial, radial, and mean diffusivity) as other indicators of white matter integrity (14,16). We assume that the investigation of white matter in never medicated patients with first episode is important for understating the core pathophysiology of schizophrenia.

The aim of this work was to study the integrity of white matter tracts connecting the frontal and temporal lobes in a group of never-medicated patients with first episode schizophrenia.

2. Material and methods

2.1. Participants

After ethical committee approval, a prospective study was conducted from January 2013 to May 2015. Twenty Egyptian patients with first episode schizophrenia who had never exposed to medication and 16 age and gender matched controls having similar socioeconomic standard and degree of education were enrolled in the study. All patients and control subjects are right handed, and have IQ above 90. All patients were diagnosed by psychiatrist using information obtained from clinical history and examination according to the diagnostic classification of DSM-IV system (23). Patients with history of head injury, neurological disorder or substance abuse that may affect the white matter integrity were excluded from the study. Patients with metal implant and claustrophobia hindering MRI examination were also excluded. MRI studies with poor image quality (e.g. due to gross motion artifact) were also excluded. All healthy participants had no history of medical or psychiatric disorder and no family history of psychiatric disorder.

2.2. MRI acquisition

MRI was conducted on 1.5 T magnet (Achieva, Philips Healthcare, Eindhoven, The Netherland) using 8-channel SENSE head coil (SENSE acceleration factor of 8). The conventional MRI included the following sequences Axial FLAIR (TR/TE/IT: 11,000/130/2800 ms), slice thickness (5 mm); 3D SPGR in the axial plane (TR/TE/FA: 22/9/30), slice thickness (1.6 mm). DTI single-shot echo-planar (TR/TE: 10,782/107) was then acquired (DTI high protocol). Diffusion weighted images in 32 non-collinear direction with $b = 800$ s/mm^2 and a baseline b0 image were obtained. Seventy axial slices with 2 mm slice thickness were obtained parallel to the anterior–posterior commissure line, with field of view of 230 mm × 230 mm and in-plain resolution = 2.5 × 2.5 × 2.5 mm.

2.3. Image analysis

DTI and conventional MRI sequences of each individual subject were transferred to offline Windows-operated personal computer for further analysis using DTI Studio software produced by this laboratory (H. Jiang and S. Mori, Johns Hopkins University and Kennedy Krieger institute, http://godzilla.kennedykrieger.org or http://lbam.med.jhmi.edu) (24). The images were first visually inspected for apparent artifact and the raw diffusion weighted images were first co-registered to b0 images and corrected for small subject motion using automatic image registration (AIR). Fractional anisotropy (FA), color FA, radial diffusivity (RD), axial diffusivity (AD) and Trace maps were then calculated in the native space (Fig. 1).

Radial diffusivity is calculated by averaging the two main Eigen values. RD is an indicator of myelin concentration. Axial diffusivity (AD) represents the diffusivity along the main eigenvector and it is an indicator of axonal integrity. Trace (a measure of overall diffusion) is the sum of diffusion in three direction and it's proportional to the mean diffusion $(\lambda_1 + \lambda_2 + \lambda_3)/3 = \text{Trace}/3$ (20,25).

2.3.1. Tract based analysis

Uncinate fasciculus and SLF are two important tracts connecting the frontal and temporal lobes. SLF is a combination of three individual pathways (the direct, anterior and posterior segments). The direct pathway of the SLF (SLFd) connects Wernicke's and Broca's territories (26). Tractography of the uncinate fasciculus (Fig. 2) and SLFd (Fig. 3) for both cerebral hemispheres was performed using two-ROI approach according to the previously described protocol with high reproducibility which was adopted by Wakana et al. using the Fiber Assignment by Continuous Tracking (FACT) method (27). The average FA, RD, AD and Trace were calculated for each tract. To study the physical properties of each tract, fiber length, volume and density were obtained. Fiber volume was calculated as the number of voxels occupied by each tract. Fiber density was calculated as the mean number of fibers per voxel.