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Research article

Alterations in white matter integrity in first-episode, treatment-naive patients with somatization disorder

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HIGHLIGHTS

- Patients with somatization disorder had reduced fractional anisotropy(FA).
- Patients with somatization disorder showed increased mean diffusivity(MD).
- Lower FA is correlated with the score of somatization subscale SCL-90.

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ABSTRACT

White matter (WM) abnormality in somatization disorder (SD) has not been reported yet. This study was designed to elucidate the alterations in WM integrity in SD. A total of 25 patients with SD and 28 healthy controls were enrolled in the study. WM integrity was analyzed using tract-based spatial statistics. No differences were found between the patients and the controls for fractional anisotropy (FA) values, mean diffusivity (MD), axial diffusivity, and radial diffusivity values at the corrected $p < 0.05$ level. Patients with SD had significantly decreased FA values in the cingulum and inferior fronto-occipital fasciculus, and significantly increased MD values in the anterior thalamic radiation and corticospinal tract compared with the controls at the uncorrected $p < 0.005$ level. Somatization severity was correlated with the FA values of the cingulum and inferior fronto-occipital fasciculus in the patients. The patients exhibit suggestive alterations in WM integrity in the cingulum, inferior fronto-occipital fasciculus, anterior thalamic radiation, and corticospinal tract.

1. Introduction

Somatization disorder (SD) is characterized by recurring, multiple, and clinically significant complaints with somatic symptoms. The somatic symptoms often refer to gastrointestinal distress, pain, and pseudoneurological symptoms [1]. The prevalence rate of SD in England has been estimated to be 0.7% [2]. Patients with SD suffer considerable disability because of illness, and impose significant burden on their caregivers, which is comparable with that observed in severe mental illnesses, such as schizophrenia and chronic depression [3]. A population-based health examination survey reported that 1.84% individuals with SD exhibit a low life quality and suffer from higher levels of emotional stress than their counterparts in the healthy subsample [4]. To date, the pathophysiology of SD remains uncertain [5].

Researchers have attempted to clarify the pathophysiology of SD using different models. One study using positron emission tomography on patients with SD, a type of somatoform disorder, shows that lower caudate glucose metabolism and lower putamen glucose metabolism are associated with severe somatization [6]; this result was in accordance with the conjecture that the central nervous system is related to SD. Neuroimaging techniques are widely used to search for evidence of altered neural function or structure that is associated with SD [7–9]. Evidence suggested that subjects who respond to thermal pain with high sensitivity have increased activation of the prefrontal cortex, anterior cingulate cortex (ACC), and somatosensory cortex [10]. Because pain is a main SD symptom, thus, this evidence may help us clarify the pathogenesis of SD.

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Grey matter abnormality is the focus of brain imaging studies for SD [9,11], and patients with SD have significantly smaller mean volumes of the left and right amygdala than healthy controls [11]. By contrast white matter (WM) abnormality in SD has not been reported. Evidence shows that SD is associated with deficits in affective theory of mind; moreover, somatic syndrome groups exhibit significantly less positive effects, and SD patients have higher level of anxiety than the controls [12]. Meanwhile, SD has been reported to be linked to the diminished capacity to consciously experience and differentiate negative affects, such as states of anger and sadness, in an adequate way [13]. Many studies have suggested that patients with anxiety or depression have significant alterations in WM integrity [14,15]. SD resembles anxiety disorders and depression, so similar changes in WM integrity in SD patients are expected. The neuronal fiber, axon and myelin sheath, the basic units of WM whose changes in architecture are related to WM integrity, can be measured by diffusion tensor imaging (DTI) [16,17].

DTI, a MRI method that allows mapping of the diffusion process of molecules in biological tissues, reveals microscopic details about tissue architecture, such as abnormalities in WM fiber structure [18]. Studies have measured the anisotropic diffusion of water in WM tracts using fractional anisotropy (FA) images in voxel-wise statistical analyses. FA is often used to reflect fiber density, axonal diameter, and myelination in WM. Moreover, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) can also be determined to investigate the different aspects of WM microstructure. Tract-based spatial statistics (TBSS) is a method that aims to improve the sensitivity, objectivity, and interpretability of the analysis of multi-subject diffusion imaging studies [19]. In the present study, we attempted to elucidate the WM integrity alterations in SD using TBSS at the individual level. We hypothesized that alterations in WM integrity in SD patients would occur. The relationships between symptom severity and FA, MD, AD, and RD were also investigated.

2. Materials and methods

2.1. Participants

Twenty-six right-handed patients, aged between 18 and 60 years, were recruited from the Mental Health Center, First Affiliated Hospital, Guangxi Medical University. All patients were diagnosed based on the Structured Clinical Interview of the DSM-IV [20]. The patients were excluded if they had a history of loss of consciousness, mental retardation, cardiovascular diseases, neurological disorders, bipolar disorder, and alcohol or substance abuse history. The patients were first-episode and drug-naive. Thirty right-handed healthy subjects were recruited from the community. No subjects met the criteria for a DSM-IV psychiatric disorder, or had a first-degree family history of psychiatric disorder. Exclusion criteria included a history of neurological disorders, DSM-IV criteria for substance misuse disorder, serious medical or surgical illness, or prior head trauma resulting in loss of consciousness and/or hospitalization.

The Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) were used to rate the symptom severity of depression [21] and anxiety [22]. The somatization subscale of symptom Checklist 90 (SCL-90) was applied to evaluate the symptom severity of somatization [23].

The two participant groups were matched on age, gender, education, and handedness. After receiving a complete description of the study, all subjects signed an informed consent form. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University.

2.2. MRI Scan Acquisition

All neuroimaging was conducted on a 3T MRI scanner (Siemens, Erlangen, Germany) at the First Affiliated Hospital, Guangxi Medical University. A single-shot, twice-refocused, spin-echo echo planar imaging sequence DTI with 30 diffusion-sensitized gradient directions was performed with the following parameters at the recruitment day: repetition time = 6100 ms; echo time = 93 ms; flip angle = 90°; slice thickness = 3 mm; field of view = 256 mm^2; matrix = 128 × 128; *b*-value = 0 and 1000 s/mm^2.

2.3. Data analysis

All DTI data processing and statistical analysis were performed using the FMRIB Software Library (FSL, version 5.06; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) [24]. All raw data were corrected for the effects of head movement and eddy currents using eddy correct to register all data to the first $b = 0$ image with affine transformation. Voxel-wise statistical analysis of the FA data was carried out using TBSS [25]. First, FA images were created by fitting a tensor model to the raw diffusion data using FMRIB's diffusion toolbox and then, brain-extracted using Brain Extraction Tool [26]. All subjects' FA data were then aligned into a common space using the FMRIB's Nonlinear Image Registration Tool, which uses a *b*-spline representation of the registration warp field. The mean FA image was created and thinned to create a mean FA skeleton, which represented the centers of all tracts common to the group. Each subject's aligned FA data was projected onto this skeleton, and the resulting data were fed into voxel-wise cross-subject statistics.

FA, MD, eigenvector, and eigenvalue maps were computed by the above procedure with the *b* vector and *b* value of gradient directions. Moreover, AD and RD maps were obtained by this step using the Threshold-Free Cluster Enhancement option with 5000 permutations. The significance level was set at $p < 0.05$ (Family Wise Error (FWE) corrected). Age, gender, and years of education were set as covariates in the main analyses. Correlation analyses at $p < 0.05$ were performed between FA and clinical variables (scores of HAMD, HAMA, and somatization subscale of SCL-90). Group comparisons of mean WM skeleton MD, AD, and RD were computed in the same manner as described above.

The differences in HAMD, HAMA, and somatization subscale of SCL-90 scores between patients and controls were estimated by the two-sample *t*-test ($p < 0.05$).

3. Results

3.1. Demographics

Inspected visually for orientation and image quality, three subjects (one patient and two healthy controls) were discarded for excessive head movement. Significant differences in HAMD, HAMA, and somatization subscale of SCL-90 scores were observed between patients and controls (Table 1). The two groups did not differ in age, sex ratio, and educational years.

3.2. WM integrity

No differences were found between patients and healthy controls for FA values, as well as between patients and healthy controls for MD, AD, and RD values (FWE corrected, $p < 0.05$, Fig. 1). In our exploratory analysis at the uncorrected level with a more conservative statistical threshold ($p < 0.005$, uncorrected), two clusters showed significantly lower FA in the SD group compared with that in the healthy group, including the right cingulum (cingulate gyrus) and right inferior fronto-occipital fasciculus; two clusters exhibited significantly higher MD in the SD group compared with that in the