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Altered structural connectivity and trait anhedonia in patients with schizophrenia

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HIGHLIGHTS

- The FA in the left cingulum and SLF were positively correlated with trait anhedonia.
- The FA in the reward system was not correlated with trait anhedonia.
- Alterations in connectivity within the DMN and CEN may be a basis of trait anhedonia.

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ABSTRACT

This study tested association between anhedonia scores and white matter integrity in order to investigate the neural basis of trait anhedonia in schizophrenia. A total of 31 patients with schizophrenia and 33 healthy controls underwent diffusion weighted imaging and scoring of trait anhedonia using the Physical Anhedonia Scale. Using tract-based spatial statistics, we found that fractional anisotropy values of some white matter regions were differently correlated with Physical Anhedonia Scale scores between the two groups. The white matter regions that were more significantly correlated with trait anhedonia in patients than in controls included the left side of the cingulum, splenium of the corpus callosum, inferior longitudinal fasciculus, superior longitudinal fasciculus I and II, anterior thalamic radiation, and optic radiation. Of these regions, fractional anisotropy values in the cingulum and superior longitudinal fasciculus II were positively correlated with trait anhedonia in patients with schizophrenia. These findings suggest that alterations in structural connectivity within large-scale brain networks, including the default mode and central executive networks, may contribute to the development of trait anhedonia in patients with schizophrenia.

1. Introduction

Disrupted connections within and between brain regions have been implicated as a central abnormality in schizophrenia [1]. In particular, growing evidence has suggested that alterations in white matter organization may play an important role in this disconnection [2]. Diffusion tensor imaging (DTI) has enabled in vivo study of white matter alterations in patients with schizophrenia. Among the measures that reflect white matter properties, fractional anisotropy (FA), the extent to which water diffusion is direction-dependent within the tissue microstructure, is the most widely used parameter [3]. FA has been reported to reflect the structural integrity of fibers, degree of myelination, and fiber coherence as decreases in FA imply damage of the myelin or axons and/or loss of coherence [3]. White matter disruptions measured by FA are widespread throughout the brain in schizophrenia, particularly in frontal and temporal regions [4]. Although most studies revealed decreased FA, some studies found increased FA in specific white matter tracts in patients with schizophrenia, compared to controls [3]. These findings of increased FA in schizophrenia were thought to reflect hyperconnectivity [5] or deficient axonal pruning [6]. Furthermore, studies using DTI have shown that white matter abnormalities are associated with specific symptoms of schizophrenia. For example, FA values of the superior longitudinal

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fasciculus were correlated with the severity of auditory hallucinations in schizophrenia [7].

Anhedonia, or reduced capacity to experience pleasure, is one of the cardinal symptoms of schizophrenia [8]. As a component of negative symptoms, anhedonia is a significant determinant of functional capacity and long-term outcome in schizophrenia [9]. The Physical Anhedonia Scale [10], which measures the extent of a decreased capacity to enjoy physical sensations, has been regarded as the standard anhedonia questionnaire in the field of psychiatry [11]. Anhedonia scores measured by the Physical Anhedonia Scale have been shown to be consistently elevated in patients with schizophrenia and have thus been identified as a trait of schizophrenia [12].

Recent neuroimaging studies have revealed that abnormalities in several brain networks in patients with schizophrenia are related to anhedonia. The reward system is known to be associated with responses to rewarding or pleasurable stimuli, and it comprises a network of brain regions including the ventral tegmental area, ventral striatum, amygdala, and orbitofrontal cortex [13]. Reduced activation in key structures of the reward system such as the ventral striatum [14–16], amygdala [14], and orbitofrontal cortex [15] have been related to more severe anhedonia. In addition, our group found that functional and structural abnormalities in the default mode network (DMN) were related to trait anhedonia in schizophrenia [17,18]. The DMN includes the ventromedial prefrontal cortex and posterior cingulate/retrosplenial cortex and is known to be responsible for self-referential processing [19]. Therefore, it was suggested to be involved in the self-referential aspect of anhedonia [17]. Considering that these brain networks require coordinated functioning of gray matter regions, it is possible that anhedonia may be the result of disrupted connectivity between gray matter regions. To date, however, the relationship between trait anhedonia and white matter abnormality has not been investigated in patients with schizophrenia.

This study was designed to investigate whether white matter alterations are associated with trait anhedonia in patients with schizophrenia. We used the Physical Anhedonia Scale to evaluate trait anhedonia and utilized FA values from DTI data as an index of the white matter integrity. We hypothesized that disruptions in white matter tracts connecting gray matter regions in the reward system and DMN are related to trait anhedonia in patients with schizophrenia.

2. Methods

2.1. Subjects

Thirty-one patients with schizophrenia (including 17 males) and 33 healthy volunteers (including 14 males) participated in this study. The two groups had no significant difference in gender or age (30.7 ± 5.9 years and 31.0 ± 7.0 years, respectively). The diagnosis of schizophrenia in patients and the exclusion of any psychiatric disorders in controls were made using the Structural Clinical Interview for the Diagnostic and Statistical Manual (DSM-IV) [20]. All participants were right-handed, and none reported any past or present medical or neurological illness or drug or alcohol abuse. The mean years of education in patients and controls (13.4 ± 2.1 years and 15.7 ± 2.6 years, respectively) were significantly different ($t = -3.8$, $df = 62$, $p < 0.001$).

The mean duration of illness in patients was 8.1 ± 6.7 years. All patients were taking one or two antipsychotic medications, and the mean chlorpromazine-equivalent dose was 398.4 ± 409.8 mg. Trait anhedonia was assessed with the Physical Anhedonia Scale [10], which comprised 61 true or false questions, with higher scores representing more severe anhedonia. Patients had significantly higher Physical Anhedonia Scale scores than controls (patients: 19.6 ± 9.3, controls: 11.9 ± 7.2, $t = 3.8$, $df = 62$, $p < 0.001$). Clinical symptoms of patients were rated using the Positive and Negative Syndrome Scale (PANSS) [21], and the mean ratings of positive, negative, and general symptom subscale scores were 15.7 ± 6.6, 16.6 ± 6.3, and 31.3 ± 10.9, respectively. The study was approved by the institutional review board, and written informed consent was obtained from all participants.

2.2. Magnetic resonance imaging

MR images were acquired using a Philips 3T scanner (Intra Achieva; Philips Medical System, Best, The Netherlands). Head motion was minimized with restraining foam pads provided by the manufacturer. Diffusion-encoded images parallel to the anterior commissure–posterior commissure line were obtained using a single-shot echo-planar acquisition with the following parameters: 128×128 acquisition matrix, 224-mm field of view, $1.72 \times 1.72 \times 2\,mm^3$ voxels, 70 axial slices, TE 71 ms, TR 7196 ms, flip angle 90°, slice gap 0 mm, 1 averaging per slice, *b*-factor of $600\,s\,mm^{-2}$, and non-cardiac gating. Diffusion-weighted images were acquired from 32 different directions with the baseline image obtained without diffusion weighting.

2.3. Image processing

Diffusion-weighted images were preprocessed using the FMRIB Software Library (FSL) 5.0.6 (http://www.fmrib.ox.ac.uk/fsl) [22]. Source data were corrected for eddy currents and head motion. FA maps were first created for each subject using the FSL. A voxelwise statistical analysis of FA data was carried out using Tract-Based Spatial Statistics (TBSS, version 1.2) [23] implemented in the FSL. The FA data were aligned into $1\,mm \times 1\,mm \times 1\,mm$ Montreal Neurological Institute (MNI) 152 spaces using the FMRIB's Nonlinear Image Registration Tool (FNIRT). Then, a mean FA image (threshold of 0.2) was created and narrowed to create a mean FA skeleton, taking only the centers of white matter tracts common to all subjects. Voxel value for the FA data of each subject was then projected onto this skeleton, and resulting data were used in the following voxelwise statistical analyses.

2.4. Statistical analysis

Voxelwise statistics were conducted with FSL Randomize program using permutation-based statistical analysis with 5000 permutations. To investigate possible confounding effects, associations in education level with FA values were tested by regression model in FSL in patients and controls, separately. In patients, association of antipsychotic doses with FA values was also tested. Then, we found that fractional anisotropy values of some white matter regions were differently correlated with Physical Anhedonia Scale scores between the two groups. FA values were regressed on anhedonia scores, along with group variable. For each voxel, the interaction between anhedonia scores and group variable was tested. Significant interaction indicates that the linear relationship between FA values and anhedonia scores significantly differs between the two groups. The results were corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE) method. The threshold for significance was set at $p < 0.05$.

To further elucidate the clinical meaning of the findings, we calculated Pearson's correlations between regional FA values and anhedonia scores in patients and controls, separately. The regions showing a significant interaction between anhedonia scores and group variable were selected for this analysis.