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Research paper

Anatomical distance affects cortical-subcortical connectivity in first-episode, drug-naive somatization disorder

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ABSTRACT

Background: Brain structural and functional alterations in the cortical-subcortical circuits have been observed in somatization disorder (SD). However, whether and how anatomical distance affects the cortical-subcortical connectivity in SD remain unclear. This study aims to examine whether anatomical distance affects the cortical-subcortical in first-episode, drug-naive SD.

Methods: Twenty-five first-episode, drug-naive patients with SD and twenty-eight healthy controls were recruited for a resting-state scan. Regional functional connectivity strength (FCS) was calculated for each voxel in the brain, which was further divided into short- and long-range FCSs. Correlation analyses were conducted between abnormal FCS and clinical/cognitive variables in the patients.

Results: Compared with the controls, the patients showed increased short-range positive FCS (spFCS) in the right superior frontal gyrus (SFG) and decreased spFCS in the left pallidum, and increased long-range positive FCS (lpFCS) in the left middle frontal gyrus and right inferior temporal gyrus (ITG). Positive correlations were observed between the spFCS values in the right SFG and Eysenck Personality Questionnaire psychoticism scores ($r = 0.441$, $p = 0.027$, uncorrected) and between the lpFCS values in the right ITG and scores of digit symbol-coding of Wechsler Adult Intelligence Scale ($r = 0.416$, $p = 0.039$, uncorrected) in the patients

Conclusions: The patients exhibited increased spFCS/lpFCS in the cortical regions and decreased spFCS in the subcortical regions. The left pallidum is first reported here to show decreased spFCS in SD. The present results suggest that abnormal cortical-subcortical circuits may play an important role in SD neurobiology.

1. Introduction

Somatization disorder (SD) is a disease with many medically unexplained somatic complaints (Rief et al., 2001). For this reason, patients with SD often visit general physicians and undergo repeated medical examinations, leading to great health care burdens (Krishnan et al., 2013). As a common psychiatric disorder, SD has a prevalence level of 4–7% in the general population (Rief et al., 2001). However, SD diagnosis is based on clinical experiences. No biomarkers have been established for clinicians to identify patients with SD, and the neurobiology underlying SD remains unclear.

Neuroimaging techniques suggest that patients with SD have brain structural and functional abnormalities in the cortical-subcortical circuits. For example, hypoperfusions in the frontal, temporoparietal, and cerebellar brain regions are revealed in SD by using a single-photon emission computed tomography machine (Garcia-Campayo et al., 2001). A positron emission tomography study reported that decreased metabolism rates in brain regions such as prefrontal cortex (PFC), anterior cingulate cortex, and insula are related to somatization in patients with major depressive disorder (Brody et al., 2001). Moreover, increased activity in the posterior cingulate cortex was observed in patients with SD by a magnetic resonance spectroscopy study (Fayed

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et al., 2012). Compared with healthy controls, patients with SD have reduced gray matter volume in the caudate nuclei (Hakala et al., 2004), amygdala (Atmaca et al., 2011), and pituitary (Yildirim et al., 2012). White matter alterations in first-episode patients with SD were not observed (Zhang et al., 2015). Recently, Su et al. (2014) found increased regional activity in the bilateral superior medial PFC and decreased regional activity in the left precuneus in patients with SD. Moreover, they observed increased functional connectivity strength (FCS) in the right inferior temporal gyrus (ITG) in the patients (Su et al., 2015). Abnormal neural activity and functional connectivity (FC) within brain regions of the default-mode network are reported in patients with SD which correlate to symptom severity and/or personality (Song et al., 2015; Su et al., 2016; Wang et al., 2016; Wei et al., 2016). The aforementioned studies reveal abnormal neural activity and FC in the brain regions of the cortical-subcortical circuits. However, the findings of these studies are inconsistent with those of concrete brain regions. The inconsistency may be attributed to a myriad of confounding factors, including sample size, sample heterogeneity, scanners, imaging parameters, and analysis methods. Despite evidence of abnormal neural activity and FC in the cortical-subcortical regions in patients with SD, the extent at which anatomical distance affects FC in the patients remains unclear. Furthermore, many studies have adopted FC analysis and focus on brain regions of interest (ROIs). The reported results are affected by the choice of ROIs, and a whole-brain analysis is urgently needed to cover the most significantly different brain regions that may represent the core pathological alterations in SD.

Human brain operates well depending on both short- and long-range FCs. Short-range FC runs at a lower metabolic- and time-cost and predominates with enhanced FCS (Salvador et al., 2005). By contrast, long-range FC runs at a higher metabolic- and time-cost (Bullmore and Sporns, 2012; Liang et al., 2013). Despite its higher metabolic- and time-cost, preferential long-range FC will not be penalized by the brain, which will result in insufficient communication (Salvador et al., 2005). Recent studies showed that anatomical distance can affect FCs in major depressive disorder (Guo et al., 2016), schizophrenia, and their unaffected siblings (Guo et al., 2014, 2015; Wang et al., 2014). Furthermore, abnormal short- and long-range FCs can be modulated by olanzapine in schizophrenia (Guo et al., 2017). However, whether and how abnormal short- and long-range FCs are present in patients with SD remain unclear.

In the present study, we constructed whole-brain FCs in samples from first-episode, drug-naive patients with SD. Specifically, the whole-brain FCs were divided into short- and long-range FCs according to their anatomical distance (Achard et al., 2006; He et al., 2007). Based on the reports that FCs increased in SD patients (Su et al., 2015; Wang et al., 2016), we hypothesized that the patients would show increased short- and long-range FCs. We also examined the correlations between abnormal FCS and clinical/cognitive variables in the patients.

2. Methods and materials

2.1. Subjects

Twenty-six right-handed patients with SD were recruited from Mental Health Center of the First Affiliated Hospital, Guangxi Medical University in China, and thirty right-handed healthy controls were recruited from the community. The subjects aged from 18 years old to 50 years old. SD diagnosis was made according to the Structured Clinical Interview of the DSM-IV (SCID) patient edition (First et al., 1997). The patients were drug-naive to antidepressants at their first visit to the psychiatric departments. The controls were screened by SCID non-patient edition (First et al., 1997). Subjects were excluded if they had severe medical or neurological diseases, mental retardation, any history of loss of consciousness, substance abuse, other psychiatric disorders, such as schizophrenia, anxiety disorders, bipolar disorders, or personality disorders, and any contraindications for MRI. The rate of comorbidity with depression was high, thus, patients who have comorbid major depressive disorder were not excluded. However, the onset of depressive symptoms should occur after the emergence of somatic symptoms in the patients. In addition, the controls were excluded if they had a first-degree relative with psychiatric disorders.

The subjects were examined with the following tests: (1) the somatization subscale of Scl-90 (Derogatis et al., 1976), Hamilton Depression Scale (HAMD, 17 items) (Hamilton, 1960), and Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) to assess the symptom severity of somatization, depression, and anxiety; (2) Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1972) to evaluate personality dimensions; and (3) Wisconsin Card Sorting Test (WCST) (Greve et al., 2005) and digit symbol coding of Wechsler Adult Intelligence Scale (WAIS) (Kaufman and Lichtenberger, 2006) to determine cognitive function.

All the subjects gave their written informed consent. The study was approved by the Local Ethics Committee of the First Affiliated Hospital, Guangxi Medical University.

2.2. Image acquisition and preprocessing

Siemens 3T scanner was used to acquire MRI images, and Data Processing Assistant for Resting-State fMRI (Yan and Zang, 2010) was applied to preprocess the images. Details of image acquisition and preprocessing are provided in the Supplementary files.

2.3. Short- and long-range FC analyses

Resting-state whole-brain FCs were analyzed on the preprocessed data. Pearson's correlation coefficients were computed between the time series of a given voxel and those of all other voxels within a gray matter mask, and the resting-state whole-brain FC matrix was obtained for each subject. The gray matter mask used in the calculations was acquired by threshing (probability > 0.2) the gray matter probability map in SPM8 (Liu et al., 2015). The FC matrices were then Fisher *z*-transformed. Regional FCS for a given voxel was computed as the sum of the connection values (*z* values) between this voxel and all other voxels within the gray matter mask, and regional FCS maps were obtained for each subject. Regional FCS maps were subsequently smoothed with an 8 mm full width at half-maximum Gaussian kernel. To examine the effects of anatomical distance on FC analyses, regional FCSs were divided into short- and long-range FCSs. The anatomical distance used to divide short- and long-range FCSs for a voxel was 75 mm according to previous studies (Achard et al., 2006; He et al., 2007). In the present study, anatomical distance between two voxels refers to the Euclidean distance between their MNI coordinates. Long-range FCS of a voxel is defined as the sum of the connections (*z* values) between this voxel and all other voxels within the gray matter mask with an anatomical distance greater than 75 mm. By contrast, the criterion of short-range FCS of a voxel is defined as the sum of the connections (*z* values) with an anatomical distance less than 75 mm. Hence, four FCS types were obtained, namely, short-range positive FCS (spFCS), short-range negative FCS, long-range positive FCS (lpFCS), and long-range negative FCS. Given the ambiguous interpretation of negative correlations (Wang et al., 2014), the analyses were restricted to positive correlations (spFCS and lpFCS). For each group, one-sample *t*-tests were performed to detect brain hubs for spFCS and lpFCS, where the FCS values were significantly greater than average. The statistical threshold was set to $p < 0.05$ for multiple comparisons using Gaussian random field (GRF) theory (voxel significance $p < 0.001$; cluster significance $p < 0.05$) with the REST software (Song et al., 2011). Union masks from the results of one-sample *t*-tests were generated for spFCS and lpFCS. Two-sample *t*-tests were conducted within the union masks from the results of one-sample *t*-tests to compare the differences between the patients and the controls. The results were GRF corrected at $p < 0.05$. FC analyses might be affected by head micromovement;