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Abnormal regional homogeneity and its correlations with personality in first-episode, treatment-naive somatization disorder

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ABSTRACT

Background: Structural and functional abnormalities of the default mode network (DMN) and their correlations with personality have been found in somatization disorder (SD). However, no study is conducted to identify regional neural activity and its correlations with personality in SD. In this study, regional homogeneity (ReHo) was applied to explore whether abnormal regional neural activity is present in patients with SD and its correlations with personality measured by Eysenck Personality Questionnaire (EPQ).
Methods: Twenty-five first-episode, treatment-naive patients with SD and 28 sex-, age-, and education-matched healthy controls participated in the whole study. During the scanning, all subjects were instructed to lie still with their eyes closed and remain awake. A ReHo approach was employed to analyze the data.
Results: The SD group had a significantly increased ReHo in the left angular gyrus (AG) compared to healthy controls. The increased ReHo positively correlated to the neuroticism scores of EPQ (EPQ-N). No other correlations were detected between the ReHo values and other related factors, such as symptom severity and education level.
Conclusions: Our results suggest that abnormal regional neural activity of the DMN may play a key role in SD with clinical implications and emphasize the importance of the DMN in the pathophysiological process of SD.

1. Introduction

Somatization disorder (SD) is characterized by a set of unexplained somatic symptoms with a prevalence of 4–7% in general population (Rief et al., 2001). The diagnosis of SD is somewhat difficult for physicians, which causes repetitively medical examinations to patients and increases health care utilization. Recent advances in neuroimaging techniques improve the possibility to explore the neural activity abnormalities associated with SD and promote the understanding of the pathophysiology of SD (Browning et al., 2011).

During the last decade, limited neuroimaging evidence has been acquired in patients with SD. Garcia-Campayo et al. found that 7 patients with SD in all of 11 patients had hypoperfusion in the right cerebellum, frontal and prefrontal regions, and temporoparietal areas using single photon emission computed tomography (SPECT) (Garcia-Campayo et al., 2001). Structural magnetic resonance imaging (MRI) studies have proposed that SD is associated with gray matter volume changes of brain regions, such as caudate nuclei (Hakala et al., 2004), amygdala (Atmaca et al., 2011), and pituitary (Yildirim et al., 2012). Evaluating glucose metabolism of four brain regions of interest, Hakala et al. observed that patients with SD had decreased glucose metabolism in caudate, putamen nuclei and thalamus (Hakala et al., 2006). Also, the dysfunction in posterior cingulate cortex, a crucial zone of the default-mode network (DMN), is disrupted during pain perception and underlies the cognitive and behavioral impairments in patients with SD accompanying with chronic pain (Fayed et al., 2012). Meanwhile, Lemche et al. found that patients with SD had altered activity of anterior ventral precuneus, posterior cingulate cortex and anteromedial thalamus when they were in happy and sad emotional states (Lemche et al., 2013). Su et al. observed that patients with SD displayed significantly increased functional connectivity strength in the right inferior temporal gyrus (Su et al., 2015), and altered neural activity in the superior medial prefrontal cortex and left precuneus (Su et al., 2014). These studies indicate that patients with SD have brain structural and functional abnormalities, especially in the DMN.

Recently, extensive work has been done in the area of resting-state fMRI. Functional connectivity is one of the most widely used methods to explore the fMRI data (Battaglia et al., 1995) and provides important information for a number of psychiatric disorders, such as schizophrenia (Anderson and Cohen, 2013; Guo et al., 2015a), depression (Guo et al., 2015b; Ma et al., 2012) and attention deficit hyperactivity disorder (Hoekzema et al., 2014). However, this method cannot provide

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information of the local regional neural activity abnormality when one region shows functional connectivity abnormality with the others. Therefore, studies are needed to examine the regional activity in patients with SD.

Regional homogeneity (ReHo) is designed to measure the similarity or synchronization of the time series of the nearest neighboring voxels. In the present study, we used Kendall's coefficient of concordance (KCC) to measure the ReHo values of the time series of a given voxel with its nearest voxels. Higher ReHo may represent neural hyperactivity in the regional area, and vice versa (Zang et al., 2004). Abnormal ReHo may indicate the disruption of temporal aspects of neural activity (He et al., 2007) and is associated with the pathophysiology of psychiatric disorders (Liu et al., 2010). The ReHo approach was well applied in psychiatric disorders such as schizophrenia, ADHD and depression (Cao et al., 2006; Chen et al., 2012; Guo et al., 2011a,b; Huang et al., 2014; Liu et al., 2006; Wu et al., 2011; Yao et al., 2009). However, no study is conducted in patients with SD using the ReHo method.

Clinically, personality traits have been revealed to correlate with the phenomenon of somatization. For example, neuroticism, a broad dimension of individual differences in the tendency to experience negative distressing emotions, is high in SD patients and related to somatization (De Gucht, 2003). Besides, the scores of Symptom Checklist 90 (SCL-90) subscales including somatization factor show a significantly positive correlation to neuroticism scores of Eysenck Personality Questionnaire (EPQ-N) (Zhang et al., 2012). Interestingly, Adelstein et al. (2011) found that extraversion and neuroticism were encoded between seed regions and the lateral paralimbic regions and dorsomedial prefrontal cortex, respectively. Lei et al. (2013) proposed that the relation between individual differences in personality and scaling dynamics in the DMN was linked with introspective cognition by resting-state fMRI. However, it remains unclear to the relationship between personality and brain activity in patients with SD. Here, we conducted a study to explore the regional brain homogeneity in patients with SD. We hypothesized that abnormal ReHo would exist in certain brain regions in SD patients. Since the DMN activity is altered in SD patients (Su et al., 2014), we expected the DMN to be particularly affected. We also expected that abnormal ReHo was correlated to personality, especially neuroticism assessed by EPQ.

2. Materials and methods

2.1. Subjects

We recruited 26 first-episode, treatment-naive patients with SD (aged from 18 to 60), and 30 age-, sex-, education-matched, right-handed healthy controls. All patients were diagnosed based on the Structured Clinical Interview of the DSM-IV (SCID) (First et al., 2012). Exclusion criteria for the participants included any history of loss consciousness, mental retardation, serious medical or neurological illness. Individuals with other psychiatric disorders such as schizophrenia, bipolar disorder or personality disorders were also excluded. Since depression is a common comorbidity in patients with SD, comorbidity with depression is allowed. None of healthy controls had serious medical or neuropsychiatric disease or major psychiatric or neurological illness in their first-degree relatives.

All subjects were assessed with EPQ (Eysenck and Eysenck, 1972) to measure personality dimensions. Hamilton depression scale (HAMD) (Hamilton, 1960), Hamilton anxiety scale (HAMA) (Hamilton, 1959) and the somatization subscale of SCL-90 (Derogatis et al., 1976) were respectively applied to assess the severity of depression, anxiety and somatic symptoms at the scan day. These scales have been validated in the Chinese patient population with high reliability and validity. Each subject signed an informed consent and the study was approved by the Ethics Committee of the First Affiliated Hospital, Guangxi Medical University.

2.2. Scan acquisition

Magnetic resonance images were collected using a Siemens 3.0 T scanner (Siemens, Erlangen, Germany). All participants were required to keep motionless with their eyes closed, and remain awake during image acquisition. Resting-state fMRI was performed using an echo-planar imaging sequence with the following parameters: repetition time/echo time (TR/TE) = 2000/30 ms, number of slice = 30, 64 × 64 matrix, 90° flip angle, 24 cm × 24 cm FOV, 4 mm slice thickness, 0.4 mm gap, and number of volumes = 250 (500 s).

2.3. Data processing

Statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) was used to preprocess image. The first 10 volumes were discarded to allow for the signal reaching equilibrium. The remaining 240 volumes were slice acquisition correction and realigned for the head motion. Participants with head movement exceeding 2.0 mm of maximum displacement in x, y, or z directions and 2.0° of angular motion were excluded. Then the fMRI images were normalized to the standard SPM8 echo-planar imaging template, and resampled to $3 \times 3 \times 3$ mm^3. The resulting fMRI data were temporally band-pass filtered (0.01–0.08 Hz) and linear detrended to reduce low-frequency drift and physiological high frequency noise.

ReHo was performed using software REST (Song et al., 2011). The formula used to calculate the KCC value has been reported previously (Zang et al., 2004). In order to reduce the effect of individual variations in KCC values, normalization of ReHo maps was done by dividing KCC among each voxel by the averaged KCC of the entire brain. The data were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum.

2.4. Statistical analyses

Chi-square test was used to compare sex ratio. Distributions of age and years of education were compared by two sample t-tests. Voxel-based comparisons of whole-brain ReHo maps were performed by using two sample t-tests. The resulting statistical maps were set at a threshold of $p < 0.05$ (corrected for multiple comparisons with a combined threshold of $p < 0.005$ and a minimum continuous cluster number of 74 voxels) using Monte Carlo simulations in the AFNI AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Linear correlations were conducted between abnormal ReHo values and psychological performances after assessing the data normality. The significance level was set at $p < 0.05$.

3. Results

3.1. Subjects

Twenty-five patients and twenty-eight healthy controls were enrolled in the study. One patient and two healthy controls were excluded due to excessive head movement. Patients with SD and healthy controls did not have significant differences in age (t-tests $t = 0.82$, $df = 51$, $p = 0.42$), sex ratio (chi-square test $x^2 = 0.25$, $df = 1$, $p = 0.61$), and educational level (t-tests $t = -0.10$, $df = 51$, $p = 0.92$). Demographic information and clinical characteristics were shown in Table 1.

3.2. ReHo: patients versus controls

Compared with healthy controls, patients with SD exhibited a significantly increased ReHo in the left angular gyrus (AG) ($t = 3.6875$, cluster size = 96 voxels). There is no decreased ReHo in any brain regions relative to healthy controls (Table 2 and Fig. 1).