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Research paper

Abnormal default-mode network homogeneity and its correlations with personality in drug-naive somatization disorder at rest

Shubao Wei [a], Qinji Su [b], Muliang Jiang [c], Feng Liu [d], Dapeng Yao [a], Yi Dai [c], Liling Long [c], Yan Song [a], Miaoyu Yu [a], Zhikun Zhang [a], Jingping Zhao [e], Wenbin Guo [a,*]

[a] Mental Health Center, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China
[b] Mental Health Institute, The 303rd Hospital of Chinese People's Liberation Army, Nanning, Guangxi 530021, China
[c] Department of Radiology, The First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi 530021, China
[d] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan 610054, China
[e] Mental Health Institute of the Second Xiangya Hospital, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha, Hunan 410011, China

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ABSTRACT

Background: While the default-mode network (DMN) appears to play a crucial role in patients suffering from somatization disorder (SD), the abnormalities of the network homogeneity (NH) of the DMN in SD patients have been poorly explored. The aim of this study is to examine DMN NH using an NH approach in patients suffering from SD at rest and determine its correlations with personality as measured by the Eysenck Personality Questionnaire (EPQ).

Methods: A total of 25 drug-naive patients with SD and 28 sex-, age-, and education-matched healthy controls underwent functional magnetic resonance imaging scans at rest. The data were analyzed by an automated NH method.

Results: Patients showed increased NH in the left superior frontal gyrus and decreased NH in the bilateral precuneus. Moreover, a significantly negative correlation was observed between the NH values in the bilateral precuneus and the EPQ-Neuroticism scores.

Limitations: The present study should be considered preliminary due to a lenient, uncorrected threshold of $p < 0.01$.

Conclusions: The results suggest that abnormal DMN NH exists in drug-naive SD and further highlight the importance of the DMN in the pathophysiology of SD.

1. Introduction

Somatization disorder (SD) is a disease with various medically unexplained somatic symptoms that last for at least 2 years. The symptoms of SD typically affect the uro-genital, cardio-respiratory, gastrointestinal, musculoskeletal system, and other internal systems. SD is a common psychiatric disorder in the general population with a prevalence level of 4–7% (Rief et al., 2001), and has a high ratio of comorbidity with anxiety and depression. As patients suffer increasing numbers of somatic symptoms, illness duration, associated depressive and anxiety symptoms, disability, and psychosocial dysfunction, SD poses an enormous medical burden (Krishnan et al., 2013). The disorder increases health-care utilization and costs with iatrogenic complication rates (Escobar et al.,1987; Smith et al., 2003; Barsky et al., 2005). Thus, it is of significant importance in public health (Gondo et al., 2012). Identification of patients with SD and providing these patients with effective treatment may improve outcomes and reduce costs.

Developments in neuroimaging techniques have allowed detailed observation of alterations in the brain that refer to the pathophysiology of SD. A Single-Photon Emission Computed Tomography (SPECT) study suggests that some SD patients show hypoperfusion in unilateral or bilateral brain regions (Javier et al., 2001). A brain [18F]-fluorodeoxyglucose-positron emission tomography (PET) study demonstrated that metabolic rates of glucose are lower in the caudate nuclei, right precentral gyrus, and left putamen in the cerebrum of SD patients compared with healthy volunteers (Hakala et al., 2002). Structural magnetic resonance imaging (MRI) studies show increased volumes in the left and right caudate nuclei (Hakala et al., 2004), but decreased volumes in the amygdala and pituitary of SD patients (Atmaca et al., 2011; Yildirim et al., 2012). Although these findings are developed

* Corresponding author.
E-mail address: guowenbin76@163.com (W. Guo).

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constantly, the current understanding of the pathophysiology of SD is inconsistent and unsatisfactory.

The emergence of new approaches to analyze functional neuroimaging data at rest has allowed a survey of the previously neglected field of intrinsic network organization (Uddin et al., 2008). Resting-state brain functions have been measured by functional magnetic resonance imaging (fMRI), a technique that has received much attention in neuroscience because of its potential to detect abnormal neural activity. Seed-based region of interest (ROI) and independent component analysis (ICA) are two methods most widely employed for analyzing the resting-state data of brain networks. Seed-based ROI is a straightforward method for testing the temporal coherence between the time series of the predefined brain region and those of all other regions via regression or correlation analyses (Biswal et al., 1995). In contrast to ROI, ICA is a model-free approach that can achieve simultaneous comparisons of activities within different brain networks (Fox and Raichle, 2007). Despite their significant benefits, however, both methods also present several disadvantages. The definition and exact placement of ROI seeds can be somewhat arbitrary, which introduces potential biases to assessment results and impedes the discovery of unexpected regions of interest. For ICA, the procedure of judging the generated components with an optimal number is relatively arbitrary, thereby greatly influencing the number of connectivity patterns that can be obtained and producing considerable variations among studies (Greicius, 2008). Regardless these issues, both methods are frequently used in the study of mental disorders, such as schizotypal personality disorder (Zhang et al., 2014) and social anxiety disorder (Liu et al., 2015).

Limited progress focused on the default mode network (DMN) in SD research has been achieved through fMRI data analysis of SD. An fMRI study reported that the severity of somatisation is correlated with regions showing high activity, including the anterior ventral precuneus (PCu; both happy and sad conditions), anteromedial thalamus (happy condition), and the posterior cingulate cortex (PCC; sad condition) (Lemche et al., 2013). Su et al. (2014) recently revealed a dissociation pattern in the DMN of SD patients based on the fractional amplitude of low-frequency fluctuations (fALFF) at rest. The fALFF value decreased in the left PCu and increased in the bilateral superior medial prefrontal cortex (MPFC). A significantly positive correlation was also observed between the *z* values of voxels in the bilateral superior MPFC and the somatization subscale of the Symptom Check List (SCL-90). Moreover, they revealed that the increase in functional connectivity strength in the right inferior temporal gyrus (ITG) of the patient group is significant in comparison with that of healthy subjects in another study (Su et al., 2015).

To date, findings in the brain of SD patients are inconsistent, and the pathophysiology of SD is largely unknown. Consequently, novel approaches for analyzing functional neuroimaging data are necessary given the shortcomings of ROI and ICA. Thus, the present study uses a novel method called network homogeneity (NH) to examine the homogeneity of the DMN for an unbiased study in SD patients. NH is a voxel-wise measure suggested by Uddin et al. (2008); it assesses the correlation of a voxel with all other voxels within a network that are specific and of interest. Homogeneity is considered as the average correlation of the time series of any given voxel with the time series of all other voxels within the network. NH is an informative approach with the potential to offer an unbiased survey of a network that is distributed and of interest through a search of pathology-related areas showing decreased network coherence. To date, NH has been well applied in study of attention deficit/hyperactivity disorder (ADHD) (Uddin et al., 2008), major depressive disorder (MDD) (Guo et al., 2014a), schizophrenia (Guo et al., 2014b) and their unaffected siblings (Guo et al., 2014c).

Interestingly, few studies have suggested that personality traits are correlated with somatization. For instance, neuroticism is a personality trait to assess individual discrepancy in the tendency to experience negative distressing emotion; this condition was found to be high in patients and related to somatization (De Gucht, 2003). In a previous study, the neuroticism scores of female respondents were found to be higher than those of male respondents, which is in line with the prevalence rate of SD. Moreover, the scores of the somatization factors included in the Symptom Checklist 90 (SCL-90) subscales showed significantly positive correlations with the neuroticism scores of the Eysenck Personality Questionnaire (EPQ-N) (Zhang et al., 2012). Wongpakaran et al. (Wongpakaran and Wongpakaran, 2014) recently demonstrated that somatization is influenced by emotional stability, vigilance, dominance, age, and education level. However, the relationship between personality traits and neural activity in SD patients remains unclear. Recently, Song et al. (2015) have observed that increased ReHo values in the left angular gyrus were significantly correlated to EPQ-N in SD patients and emphasized the importance of the DMN in the psychopathology of SD.

In the current study, we explored the NH of DMN in patients with drug-naive SD. Based on previous findings focused on the DMN (Song et al., 2015), we hypothesized that patients with SD would show alterations of NH in the DMN. We also expected that there were significant correlations between the abnormal NH and personality traits, especially neuroticism.

2. Materials and methods

2.1. Subjects

The study was conducted in an outpatient setting at the First Affiliated Hospital, Guangxi Medical University, China. A total of 26 right-handed SD patients, aged 18–50 years were originally recruited into the study. SD was diagnosed using the Structured Clinical Interview in accordance with the DSMIV (First et al., 1997). The patients were at their contact with psychiatric outpatient setting and medication-naive to antidepressants. Exclusion criteria for the patients were: (1) mental retardation, (2) substance abuse, (3) any history of serious medical or neurological illness, (4) any history of loss consciousness, and (5) any lifetime psychiatric disorders such as schizophrenia, bipolar disorders, anxiety disorders, and personality disorders. Given the high rate of comorbidity with depression in patients with SD, comorbidity with depression was allowable. Six patients had comorbidity with major depressive disorder. However, depressive symptoms occurred after the emergence of somatic symptoms in these patients.

A total of 30 age-, sex-, and education-matched healthy controls were recruited from the community. The controls were required to have no craniocerebral operations, no history of severe neuropsychiatric diseases, no serious medical illness, and no family history of neurological or major psychiatric disorder in their first-degree relatives. Participants who had any contraindications for fMRI were excluded.

All participants were evaluated with EPQ (Eysenck and Eysenck, 1972) to measure personality dimensions. Somatic symptom severity, anxiety and depression were respectively evaluated by the somatization subscale of SCL-90 (Derogatis et al., 1976), Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) and the 17-item Hamilton rating scale (HAMD) (Hamilton, 1960). The reliability and validity of the four scales were above 0.8. Written informed consent was obtained from each subject after introductory information on the procedure was given. The ethics committee of the First Affiliated Hospital of Guangxi Medical University approved the study.