Clinical Neurophysiology 126 (2015) 1711–1716

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Disrupted cortical hubs in functional brain networks in social anxiety disorder

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ARTICLE INFO

Article history:
Accepted 19 November 2014
Available online 27 November 2014

Keywords:
Graph theory
Resting-state fMRI
Hub
Fusiform gyrus
Precuneus
Social anxiety disorder/social phobia

HIGHLIGHTS

- We use functional connectivity strength to examine the cortical hubs in social anxiety disorder (SAD).
- Patients with SAD have disrupted cortical hubs during resting state.
- The findings provide novel insight into the pathophysiological mechanisms of SAD.

ABSTRACT

Objective: The network hubs, characterized by the large number of connections to other regions, play important roles in the proper and effective transfer of information. Previous functional neuroimaging studies have demonstrated that patients with social anxiety disorder (SAD) have aberrant functional connectivity. The changing pattern in functional network hubs in SAD, however, remains incompletely understood.
Methods: Twenty SAD patients and 20 matched healthy controls were recruited. Resting-state fMRI data were obtained using a gradient-recalled echo-planar imaging sequence. Whole-brain voxel-wise functional networks were constructed by measuring the temporal correlations of each pair of brain voxels and then hubs were identified by using the graph theory method. Specifically, a functional connectivity strength (FCS) map was computed in each subject and the regions with higher FCS value were considered as functional network hubs.
Results: Compared with healthy controls, SAD patients showed significantly decreased FCS in the bilateral precuneus and significantly increased FCS in the right fusiform gyrus. Furthermore, a significantly negative correlation was observed between the FCS value in the precuneus and the illness duration.
Conclusion: The present study demonstrated for the first time that disrupted cortical hubs existed in patients with SAD during resting state.
Significance: These findings may provide novel insight into understanding of pathophysiological mechanisms underlying SAD.

1. Introduction

Social anxiety disorder (SAD), recognized as a discrete anxiety disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994), is characterized by fear and avoidance in social situations. SAD is typically the second most common

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http://dx.doi.org/10.1016/j.clinph.2014.11.014
1388-2457/

anxiety disorder, and the lifetime prevalence of SAD is 12.1% (Kessler et al., 2005a,b). People with SAD typically suffer significant emotional distress and functional impairment at work and in social domains. However, the pathophysiological mechanisms of SAD, until now, remain unknown.

Rapid advances in neuroimaging techniques pave a new way for providing a deeper understanding of the pathophysiology of SAD. Task-based fMRI studies have observed that SAD patients exhibit regional hyperactivity and altered functional connectivity. For example, a prior study has documented hyperactivity in the bilateral fusiform gyrus and greater connectivity between the fusiform gyrus and amygdala during processing of fearful faces (Frick et al., 2013). Moreover, a meta-analysis has found that SAD patients showed hyperactivity in the fusiform gyrus when faced with negative emotional stimuli (Etkin and Wager, 2007). These findings imply a pivotal role of the fusiform gyrus in SAD neuropathology.

Recently, resting-state fMRI has attracted considerable attention and has been successfully used to investigate the brain function in clinical populations (Chen et al., 2012; Guo et al., 2011; Liu et al., 2013b; Su et al., 2014). The main advantage is that resting-state fMRI is not susceptible to potential performance confounding from a task, and it can be applied to subjects incapable of performing cognitive tasks such as neonates and patients with reduced consciousness (Greicius, 2008). Resting-state functional connectivity has emerged as a powerful approach to investigate mental disorders. To date, several studies have investigated resting-state functional connectivity related to SAD. For example, Hahn et al. (2011) find a significantly decreased functional connectivity between posterior cingulate cortex (PCC)/precuneus and amygdala in SAD patients, and the connectivity strength was negatively correlated with anxiety scores, suggesting the significance of a modulatory influence of the PCC/precuneus onto the amygdala. Our group observes that the precuneus has reduced functional connectivity in SAD patients, supporting the hypothesis that this region is able to suspend functional connectivity within the default mode network (Liao et al., 2010). Furthermore, we have found that the precuneus exhibits high weight for classifying SAD from healthy controls (Liu et al., 2013a).

The human brain is a complex, interconnected system that supports efficient processing and integration of information, and a network is defined as a set of nodes linked by connections (Bullmore and Sporns, 2009). Within the brain network, most nodes have just a few connections, but some nodes have an unusually large number of connections (or large degree) and can be considered as hubs (Achard et al., 2006). Evidence for brain hubs comes from both structural and functional network analyses in human (Hagmann et al., 2008; He et al., 2009). Hubs play central roles in integrating diverse informational sources and supporting fast communication with minimal energy cost (Bassett and Bullmore, 2006). Thus, if the hubs were disrupted, the brain network would be severely damaged. Although previous studies have demonstrated altered functional connectivity in SAD, the changing pattern in functional network hubs in SAD remains largely unclear.

Motivated by previous work, we investigated the functional brain hubs in SAD. To identify candidate hubs, the simplest graph measure is the node degree, also termed as degree centrality (van den Heuvel and Sporns, 2013; Wasserman, 1994). Recently, resting-state fMRI has been used to detect functional hubs of human brain networks by computing the functional connectivity strength (FCS) at the voxel level, that is, the average functional connectivity between a given voxel and all other voxels in the brain (Cole et al., 2010; Liang et al., 2013). Such an FCS measure is known as the "degree centrality" of weighted networks in terms of the graph theory (Buckner et al., 2009). On the basis of the aforementioned functional connectivity studies, we hypothesized that SAD patients might have increased FCS in the fusiform gyrus and decreased FCS in the precuneus as compared to healthy controls.

2. Methods

2.1. Subjects

Twenty-three patients with SAD aged 20–33 years and 20 age-, gender-, and education-matched healthy controls were recruited from the Mental Health Center of the Huaxi Hospital, Sichuan University, Chengdu, China. This study was approved by the local ethical committee of the Huaxi Hospital, and written informed consent was obtained from each subject before any study procedure was initiated. The diagnosis of SAD was made with the Structured Clinical Interview DSM-IV (SCID)-Patients Version by two attending psychiatrists and a trained interviewer. Patients with SAD did not receive any psychotherapy or psychiatric medications. The exclusion criteria included the following: (1) a history of psychiatric and neurological disease and diagnosis of other mental disorders except SAD; and (2) existence of organic brain disorder, drug or alcohol abuse, pregnancy, or any physical illness such as brain tumor, hepatitis, and epilepsy as assessed based on the medical records. In addition, no gross abnormalities in brain MRI scans (i.e., T1- and T2-weighted images) were found for any of the subjects inspected by an experienced neuroradiologist. All healthy controls were screened by the same psychiatrists and interviewer. None of them had a history of neurological or psychiatric disorders or a history of major psychiatric or neurological illness in their first-degree relatives. All subjects of the two groups were evaluated with the Spielberger State-Trait Anxiety Inventory (STAI), the Hamilton Depression Rating Scale (HAMD), the Hamilton Anxiety Rating Scale (HAMA), and the Liebowitz Social Anxiety Scale (LSAS). Of note, the STAI questionnaire consists of two components: the STAI-Trait (STAI-T) score, measuring the level of inherent trait anxiety of the subject, and the STAI-State (STAI-S) score, measuring the level of state anxiety at the time of completing the test. The STAI-S scores were obtained immediately before and after the MRI scanning (pre-scanning and post-scanning) (Campbell et al., 2007).

2.2. Data acquisition

Scanning took place on the 3.0-T GE scanner (Excite, General Electric, Milwaukee, WI, USA) in the Huaxi MR Research Center of Sichuan University, Chengdu, China. Foam padding and headphones were used to minimize head movement and reduce the scanner noise, respectively. During the scanning, the participants were instructed to hold still and rest with their eyes closed but not fall asleep. A total of 205 volumes were acquired using a single-shot, gradient-recalled echo-planar imaging (EPI) sequence. Five dummy scans were discarded to ensure stable magnetization and the remaining 200 volumes were used for the following analyses. The acquisition parameters were as follows: repetition time = 2000 ms; echo time = 30 ms; thickness = 5 mm, without slice gap; field of view = 240 × 240 mm; flip angle = 90°; in-plane matrix = 64 × 64; 30 axial slices; and voxel size = 3.75 × 3.75 × 5.00 mm.

2.3. Data preprocessing

Functional image data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Yan and Zang, 2010). Briefly, the fMRI time series were first corrected for within-scan acquisition time differences between slices and realigned to the first functional scan to correct for head motion.