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Disrupted cortical hubs in functional brain networks in social anxiety disorder

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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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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.

The participants with head movement exceeding 2.0 mm of translation or 2.0° of rotation in any direction were excluded. In addition, the *mean motion* (the root mean squares of both overall head motion displacement and rotation) was further computed to determine the comparability of head movement across groups (Liu et al., 2012; Van Dijk et al., 2012). All the realigned images were spatially normalized to the Montreal Neurological Institute EPI template in SPM8 and each voxel was resampled to $3 \times 3 \times 3$ mm^3. To avoid introducing artificial local spatial correlations, the images were not smoothed (Liu et al., 2014). The time series were further linearly detrended and temporally band-pass-filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency physiological noises. After this, a signal from a region centered in the white matter, a signal from a ventricular region of interest, and six rigid-body head motion parameters were regressed out from the data. The fluctuations unlikely to be involved in specific regional correlations were removed by using this procedure. The residuals of these regressions were used for the following functional connectivity analysis.

2.4. Whole brain voxel-wise functional connectivity analysis

For each subject, the FCS value was calculated for each voxel (i.e., the seed) by first extracting its time series, and then the Pearson's correlations between the time series of the seed and all other voxels' time series were calculated as follows:

$$r_{i,j} = \frac{\sum_{t=1}^{T}[x_i(t) - \bar{x}_i] \cdot [x_j(t) - \bar{x}_j]}{\sqrt{\sum_{t=1}^{T}[x_i(t) - \bar{x}_i]^2}\sqrt{\sum_{t=1}^{T}[x_j(t) - \bar{x}_j]^2}}$$

where $x_i(t)$ and $x_j(t)$ $(t = 1, 2, \cdots, T,\ T = 200)$ were the time series of voxel i and j with means of $\bar{x}_i$and $\bar{x}_j$, respectively. It was worth noting that the functional connectivity computation was constrained within a binary gray matter mask, which was created by SPM8's gray matter probability template. Specifically, each voxel in this template has a probability value that represents the probability of this voxel belonging to gray matter. Consistent with DPARSF (Yan and Zang, 2010), we used a threshold of 0.2 to create a gray matter mask, which means voxels with the probability >0.2 will be classified as gray matter. In addition, according to Wang et al. (2014), we set a threshold of 0.2 to remove weak correlations possibly arising from signal noise. The correlation coefficients greater than this threshold were averaged over the gray matter mask, and then the mean value was stored back in the seed voxel. The whole process was repeated for all other voxels. Thus, we could obtain a 3D FCS map for each subject. Subsequently, the FCS map was converted to z scores and spatially smoothed with a 6-mm full width at half-maximum Gaussian kernel.

2.5. Statistical analyses

One-tailed one-sample t-tests were performed within each group to identify the brain hub regions where the FCS value was significantly larger than average. The significant threshold was set at $p < 0.05$ (multiple comparison using the topological false discovery rate (FDR) criterion (Chumbley et al., 2010)). This correction was confined within the aforementioned gray matter mask. To find the disrupted brain hub regions, two-tailed two-sample t-tests ($p < 0.05$, topological FDR corrected) were then performed to compare the FCS maps between the SAD and control groups within a specified mask. This mask was created by combining the significant clusters in both groups, which were obtained from one-sample t-test results. The abovementioned t-tests were performed with gender, age, years of education, and head motion as covariates as these factors may confound the results (Zuo et al., 2012).

Furthermore, linear correlation analyses were performed to explore the relationship between the alteration of FCS and clinical variables in the SAD group. Specifically, correlations between the mean FCS values within regions showing significant between-group FCS differences and LSAS (total score, fear factor and avoidance factor) and illness duration were analyzed, and the significance levels were set at $p < 0.05$. Gender, age, years of education, and head motion were also considered unconcerned, confounding factors in the correlation analyses. As the correlation analyses were exploratory in nature, we did not perform multiple comparison correction.

3. Results

3.1. Demographics and clinical characteristics of the participants

The demographic and clinical data are presented in Table 1. Data from three patients were excluded for further analyses due to excessive head motion. Gender (14 males for the SAD group and 14 males for the control group), age (22.90 ± 3.99 years for the SAD group; 21.75 ± 3.73 years for the control group; $t(38) = 1.02$, $p = 0.313$), the years of education (14.10 ± 1.48 years for the SAD group; 14.05 ± 1.96 years for the control group; $t(38) = 0.091$, $p = 0.928$), and the head motion (0.034 ± 0.012 mm for the SAD group; 0.04 ± 0.02 mm for the control group; $t(38) = -1.15$, $p = 0.258$) were matched between patient and control groups. Compared with healthy controls, patients with SAD had significantly higher scores on the LSAS (total score, fear factor, and avoidance factor), HAMD, HAMA, STAI-T, and pre-scanning STAI-S.

3.2. Within-group and between-group FCS analyses

The results derived from one-sample t-tests for SAD and control groups (one-tailed one-sample t-tests; $p < 0.05$, topological FDR corrected) are shown in Fig. 1. Functional hubs were found mainly in the posterior medial and parietal cerebral cortex as well as several temporal–occipital and frontal modules. In addition, the insula and visual regions were also among the functional hubs. These findings were consistent with previous studies (Achard et al., 2006; Buckner et al., 2009; Hagmann et al., 2008; Liang et al., 2013). Moreover, the results obtained from the two-tailed two-sample t-tests showed significant differences in FCS between two groups ($p < 0.05$, topological FDR corrected). As shown in Table 2 and Fig. 2, the SAD group showed significantly decreased FCS in

Table 1
Demographics and clinical characteristics of patients with SAD and healthy controls.

Variables (Mean ± SD)	SAD	HC	p value
Gender (M/F)	20 (14/6)	20 (14/6)	–
Age, years	22.90 ± 3.99	21.75 ± 3.73	0.313
Education, years	14.10 ± 1.48	14.05 ± 1.96	0.928
Illness duration, months	45.40 ± 39.78	–	–
LSAS			
Total score	53.90 ± 11.50	20.00 ± 8.27	<0.001
Fear factor	28.00 ± 6.17	8.40 ± 4.81	<0.001
Avoidance factor	25.90 ± 6.93	11.60 ± 5.91	<0.001
HAMD	7.50 ± 6.27	1.30 ± 1.87	<0.001
HAMA	6.20 ± 4.74	1.22 ± 1.80	<0.001
STAI			
STAI-T	48.25 ± 7.02	32.90 ± 4.93	<0.001
STAI-S			
Pre-scanning	41.35 ± 8.31	31.40 ± 4.85	<0.001
Post-scanning	37.65 ± 9.54	33.10 ± 7.08	0.095
Head motion	0.034 ± 0.012	0.040 ± 0.020	0.258

Abbreviations: SAD, social anxiety disorder; HC, healthy controls; LSAS, Liebowitz Social Anxiety Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; STAI, State-Trait Anxiety Inventory.
The p values were obtained using two-sample t-tests.

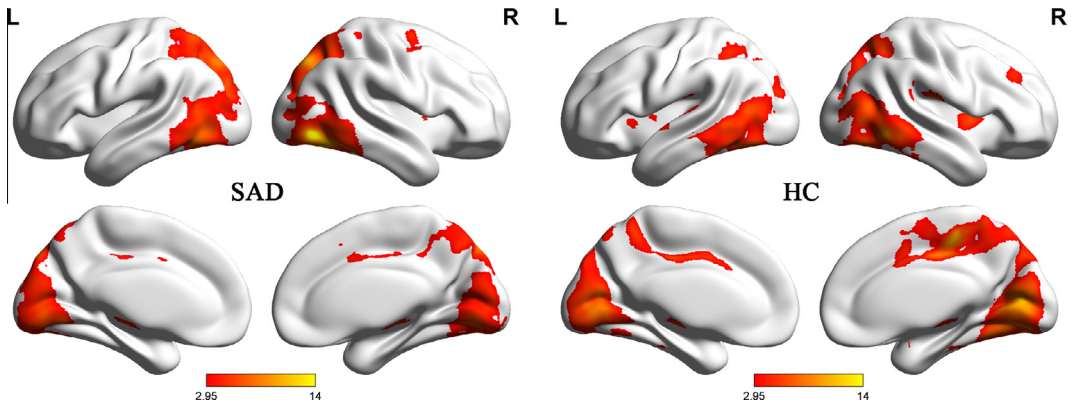

Fig. 1. Results of hub identification by one-tailed one-sample *t*-tests for SAD group (left panel) and HC group (right panel). The threshold was $p < 0.05$ with topological FDR corrected. The color bar represents the *t* value of the within-group analysis. SAD, social anxiety disorder; HC, healthy controls; L, left; R, right.

Table 2
FCS differences between the patients with SAD and HC.

Brain regions	Cluster size (mm^3)	MNI coordinates (mm)			*T* value
		x	*y*	*z*	
SAD > HC					
Right fusiform gyrus	1917	42	−60	−15	5.28
SAD < HC					
Bilateral precuneus	3834	3	−48	63	−3.79

SAD, social anxiety disorder; HC, healthy controls; FCS, functional connectivity strength; MNI, Montreal Neurological Institute.

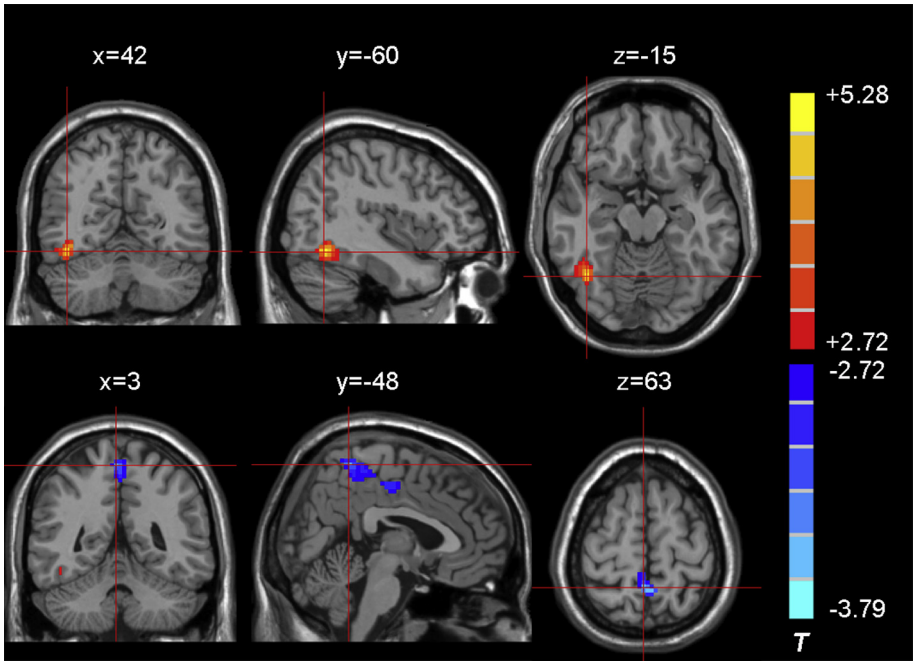

Fig. 2. FCS differences by two-tailed two-sample *t*-tests between patients with SAD and healthy controls. The threshold was $p < 0.05$ with topological FDR corrected. The color bar represents the *t* value of the between-group analysis.

the bilateral precuneus and significantly increased FCS in the right fusiform gyrus as compared to healthy controls.

3.3. Correlation analyses

As shown in Fig. 3, the FCS value in the precuneus had a significantly negative correlation with illness duration in the SAD patients ($r = -0.5294$, $p = 0.0164$). However, no other significant correlation was found in the SAD group.

4. Discussion

To the best of our knowledge, this is the first study to investigate the disrupted brain functional hubs in patients with SAD. Although both groups showed similar hub distributions, compared with healthy controls, the SAD group showed significantly decreased FCS in the bilateral precuneus and significantly increased FCS in the right fusiform gyrus. Furthermore, the abnormal FCS in the precuneus was significantly negatively correlated

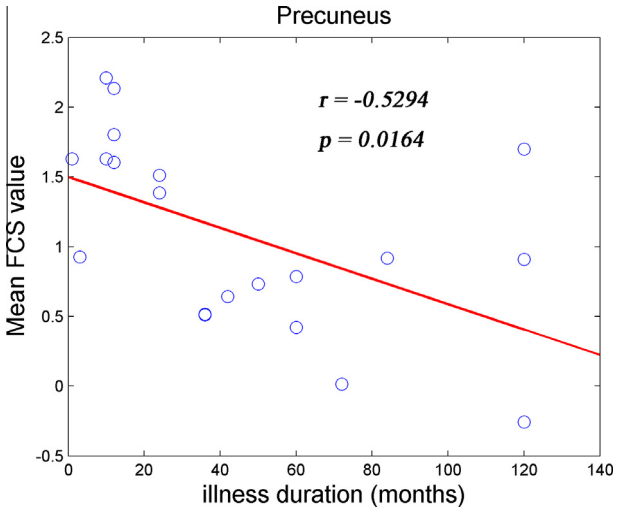

Fig. 3. Correlation between regions with significantly altered FCS and illness duration. FCS, functional connectivity strength.

with illness duration, which may have clinical implications for observation of SAD.

The precuneus was found to exhibit decreased FCS in patients with SAD. Actually, the precuneus is not only a central node in the human brain (Hagmann et al., 2008) but also a critical hub of the default mode network (Utevsky et al., 2014). The network mainly includes the medial prefrontal cortex, PCC/precuneus, and inferior parietal lobule, which is shown to decrease in connectivity during attention-demanding tasks and increasing during rest (Fox et al., 2005; Raichle et al., 2001). This network is considered a high-level cognitive network, and it plays a significant role in the self-consciousness and self-related mental representations (Cavanna and Trimble, 2006). In line with our finding, previous studies have found decreased functional connectivity related to this region by using a seed-based functional connectivity method and independent component analysis (Hahn et al., 2011; Liao et al., 2010). Furthermore, we found that the FCS value in the precuneus was negatively related to illness duration. These findings indicated that the precuneus may be closely related to the pathophysiology underlying SAD.

As a central node of the face perception network, the fusiform gyrus is an important region implicated in social functions such as face recognition (Haxby et al., 2000). The face perception network has been indicated to be involved in the neuropathology of SAD, with abnormal activity being associated with increased social anxiety (Pujol et al., 2009; Straube et al., 2004). Previous studies have reported involvement of this region in face processing and the altered processing of emotional faces in SAD (Freitas-Ferrari et al., 2010; Haxby et al., 2000). Recently, several studies have demonstrated hyperactivity in the fusiform gyrus (mainly the right fusiform gyrus) based on task-based fMRI. For example, Straube et al. (2004) have observed that SAD is associated with bilateral fusiform hyperactivity to emotional faces; Etkin and Wager (2007) have found right fusiform hyperactivity to negative emotional stimuli in SAD; and Frick and colleagues (Frick et al., 2013) have reported that patients with SAD have enhanced reactivity in the bilateral fusiform gyrus to fearful over neutral faces, implying a central role of the fusiform gyrus in SAD neuropathology. Furthermore, the increased FCS region was located in the fusiform face area. This area serves to process facial information (Kanwisher et al., 1997, 1999) and exhibits a right-hemispheric dominance in the human brain (Barton et al., 2002; Pitcher et al., 2007). These studies provide further supports for our findings of abnormal FCS in the right fusiform gyrus.

Several limitations should be considered in explaining the findings. First, we used a relatively low sampling rate (TR = 2 s) for multislice acquisitions. Under this sampling rate, respiratory and cardiac fluctuations were reduced but they could not be completely eliminated. Moreover, it is commonly seen that patients with anxiety show higher respiratory and cardiac fluctuations, and thus these artifacts should be compared between groups in this study. However, we did not record these data during scanning. Therefore, we could not assess the influence of these factors on the present results, and this was a limitation of the current study. Second, although many graph metrics could be used to identify the functional hubs of brain networks, we employed FCS because it was difficult to calculate other graph metrics (e.g., betweenness or efficiency) due to a highly computational load in a >60,000-node network. Further study is needed to use high-performance computing systems to calculate other graph metrics of voxel-based brain networks. Third, it is still an ongoing controversy of removing the whole brain global signal in the preprocessing of resting-state fMRI data (Fox et al., 2009; Murphy et al., 2009; Saad et al., 2012). Saad et al. (2012) have demonstrated that global signal regression can dramatically alter correlation patterns, potentially spreading underlying group differences to regions that may never have had any correlation. Therefore, we did not regress out the global signal. Further studies are needed to determine whether the global signal should be removed. Finally, the decreased FCS in the precuneus had a significantly negative correlation with the illness duration rather than the severity. Thus, it was possible that the change in the precuneus might be a secondary change, instead of the casual factor of SAD.

5. Conclusion

In conclusion, the present study demonstrated for the first time that the SAD was associated with disrupted cortical hubs in functional brain networks. Specifically, significantly decreased FCS in the bilateral precuneus and significantly increased FCS in the right fusiform gyrus were observed in the SAD patients. Furthermore, a significantly negative correlation was found between the FCS value in the precuneus and the illness duration. These findings may open a novel way to better understand the pathophysiological mechanisms of SAD. The disrupted cortical hubs along with the significant correlation suggested that the network hubs with rich connections were preferentially targeted in SAD. Future work combining multimodal imaging data may help to provide further valuable information about this disorder.

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Conflict of interest: All authors declare that they have no conflicts of interest.

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