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Selective aberrant functional connectivity of resting state networks in social anxiety disorder

Wei Liao [a], Huafu Chen [a,*], Yuan Feng [b], Dante Mantini [c], Claudio Gentili [d], Zhengyong Pan [a], Jurong Ding [a], Xujun Duan [a], Changjian Qiu [b], Su Lui [e], Qiyong Gong [e,*], Wei Zhang [b]

[a] Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, PR China
[b] Mental Health Center, West China Hospital of Sichuan University, Chengdu 610041, PR China
[c] Laboratory of Neuro-psychophysiology, K. U. Leuven Medical School, Leuven, Belgium
[d] Unit of Clinical Psychology, AUO Pisa, Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies, University of Pisa, Via Roma 67, 56126 Pisa, Italy
[e] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, West China School of Medicine, Chengdu 610041, PR China

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ABSTRACT

Several functional MRI (fMRI) activation studies have highlighted specific differences in brain response in social anxiety disorder (SAD) patients. Little is known, so far, about the changes in the functional architecture of resting state networks (RSNs) in SAD during resting state. We investigated statistical differences in RSNs on 20 SAD and 20 controls using independent component analysis. A diffuse impact on widely distributed RSNs and selective changes of RSN intrinsic functional connectivity were observed in SAD. Functional connectivity was decreased in the somato-motor (primary and motor cortices) and visual (primary visual cortex) networks, increased in a network including medial prefrontal cortex which is thought to be involved in self-referential processes, and increased or decreased in the default mode network (posterior cingulate cortex/precuneus, bilateral inferior parietal gyrus, angular gyrus, middle temporal gyrus, and superior and medial frontal gyrus) which has been suggested to be involved in episodic memory, and self-projection, the dorsal attention network (middle and superior occipital gyrus, inferior and superior parietal gyrus, and middle and superior frontal gyrus) which is thought to mediate goal-directed top-down processing, the core network (insula-cingulate cortices) which is associated with task control function, and the central-executive network (fronto-parietal cortices). A relationship between functional connectivity and disease severity was found in specific regions of RSNs, including medial and lateral prefrontal cortex, as well as parietal and occipital regions. Our results might supply a novel way to look into neuro-pathophysiological mechanisms in SAD patients.

Introduction

Social anxiety disorder (SAD) is a common mental disorder (Stein and Stein, 2008), which is thought to involve emotional hyperactivity, cognitive distortions, and ineffective emotion regulation (Goldin et al., 2009). Epidemiological studies conducted on general population have pointed out that the lifetime prevalence of SAD ranges between 4.0% and 16% (Ohayon and Schatzberg, 2010). Findings from neurophysiological and brain-imaging studies (Damsa et al., 2009; Engel et al., 2009) have showed that patients with SAD exhibit greater activity than healthy subjects in several areas related to emotional process as the amygdala and insula during social fear and anxiety conditioning (Etkin and Wager, 2007; Phan et al., 2006; Stein et al., 2002; Tillfors et al., 2001), suggesting the presence in SAD of impaired cortico-limbic circuit that mainly involves medial prefrontal cortex and limbic regions (Phan et al., 2006; Stein et al., 2002; Tillfors et al., 2001). Moreover, abnormal activation in the fusiform gyrus, striatal regions, superior temporal gyrus, orbital prefrontal cortex, and inferior frontal gyrus (Gentili et al., 2008; Sareen et al., 2007; Tillfors et al., 2002) were also observed in this disease. These widely distributed differences in brain activity during tasks suggest that brain functional abnormalities are not related to a single region dysfunction but to a wider network dysfunctions. As a matter of fact, however, traditional activation paradigms and multiple regression analysis cannot assess network connectivity and its dysfunction. Thus, a better understanding of the neurobiology of SAD would require investigations at different brain network levels, even during a resting state condition (Etkin et al., 2009). These would allow to assess possible differences in the crosstalk among brain regions that could represent the baseline antecedent of abnormal activations in response to given tasks.

* Corresponding authors. H. Chen is to be contacted at Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, PR China. Fax: +86 28 83208238. Q. Gong, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital/West China School of Clinical Medicine, Guo Xuexiang 37#, Chengdu 610041, PR China.
E-mail addresses: chenhf@uestc.edu.cn (H. Chen), qygong05@126.com (Q. Gong).

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Resting state brain networks were often shown to present abnormalities in many neuropsychiatric disorders (Calhoun et al., 2008; 2009; Garrity et al., 2007; Greicius et al., 2004; 2007; Mohammadi et al., 2009; Seeley et al., 2009; Sorg et al., 2007). These abnormalities mostly relate to the alterations of coherent intrinsic neuronal activity of blood oxygen level-dependent (BOLD) fluctuations observed in the resting state by functional magnetic resonance imaging (fMRI) (Fox et al., 2005). Functional connectivity investigations documented that intrinsic brain activity in the resting state is spatially organized in a set of specific coherent patterns (Beckmann et al., 2005; Damoiseaux et al., 2006; 2008; De Luca et al., 2006; Jafri et al., 2008; Liao et al., 2010; Mantini et al., 2007). Interestingly, such patterns, namely resting state networks (RSNs), recapitulate the functional architecture of somato-motor, visual, auditory, attention, language, and memory networks that are commonly modulated during active behavioral task (Corbetta and Shulman, 2002; Fox et al., 2006; Mantini et al., 2009). Among them, the default mode network (DMN) would be of considerable interest, as it consistently increased activity during rest than cognitive tasks (Raichle et al., 2001). A previous study in anxiety patients showed a reduced deactivation of the medial prefrontal cortex (MPFC) and an increased deactivation of the posterior cingulate cortex (PCC) during listening to threat-related words as compared to resting condition (Zhao et al., 2007). These two brain regions are critical in the DMN (Broyd et al., 2009; Buckner et al., 2008). In addition, findings from fMRI and single photon emission computed tomography (SPECT) studies consistently implicate alterations of critical regions in DMN in patients with SAD (Gentili et al., 2009; Warwick et al., 2008). More recently, a pioneering resting state functional connectivity study has demonstrated that increased connectivity of a fronto-parietal network (namely executive control network) and decreased connectivity of insula-cingulate network (namely salience network) in generalized anxiety disorder (Etkin et al., 2009).

Little is known, so far, about the changes in the functional architecture of RSNs in SAD during resting state. In previous task-related studies, single regions devoted to perception, attention, meaning attribution, self-focused attention, social cognition and emotions those functions were found differentially activated in SAD patients as compared to healthy controls. These differential activations could be explained just in terms of aberrant regional responses, but alternatively they may reflect 'normal responses within a dysfunctional network'. In this regard, investigations on RSNs in SAD patients could provide valuable data to validate the network impairment hypothesis. In the present study, we assessed the topological differences of the RSNs between SAD patients and healthy controls, using independent component analysis (ICA) on resting state fMRI data. The primary aims of the present work are to test: 1) whether the functional connectivity of any RSNs might be aberrant in SAD patients and 2) if so, whether these changes are related to the measured clinical severity. The results of this study may supply a novel way to look into the neuro-pathophysiological mechanisms of SAD.

Methods and materials

Subjects

A first study group was composed of 20 patients (22.90± 2.99 yrs, all right-handed) who were recruited through the Mental Health Center of the Huaxi Hospital, Chengdu, China (Table 1). Diagnosis of SAD was determined by consensus between the two attending psychiatrists and a trained interviewer using the Structured Clinical Interview DSM-IV (SCID)-Patients Version. Other inclusion/exclusion criteria were: no history of neurological and psychiatric disease and no diagnosis of other mental disorders except SAD. SAD patients did not receive psychotherapy and psychiatric medications. A second group was composed of 20 age-, sex-, education-matched healthy controls (HC) (21.65± 3.57 yrs, all right-handed) was recruited and screened using the SCID-Patients Version to confirm the current absence of psychiatric and neurological illness. Additionally, healthy controls were interviewed to confirm that there was no history of psychiatric illness among their first-degree relatives. All participants of the two groups were evaluated with the Liebowitz Social Anxiety Scale (LSAS), Spielberger State-Trait Anxiety Inventory (STAI), Hamilton Anxiety Rating Scale (HAMA), and Hamilton Depression Rating Scale (HAMD). According to previous studies LSAS does not substitute a clinical interview for the diagnosis of social anxiety even if a score over 30 indicates a probable diagnosis of social anxiety while a score over 60 indicates a probable diagnosis of generalized social anxiety (Liebowitz, 1987).

Table 1
Psychological or behavioral data.

	SAD ($n=20$)	HC ($n=19$)	SAD vs. HC	
	M± SD	M± SD	*T* value	*p* value
Gender (*n*: male/female)	14M/6F	14M/5F	–	.801[a]
Age (yrs)	22.90± 3.99	21.89± 3.77	.91	.369
Education (yrs)	14.10± 1.48	14.11± 2.00	−.01	.993
Duration (mths)	45.40± 39.78	–	–	–
LSAS				
Total score	53.90± 11.50	19.21± 7.68	11.02	<.0001
Fear factor	28.00± 6.17	8.42± 4.94	10.90	<.0001
Avoidance factor	25.90± 6.93	10.79± 4.79	7.88	<.0001
HAMD	7.50± 6.27	1.05± 1.54	4.36	<.001
HAMA	7.50± 6.27	.89± 1.52	4.65	<.0001
STAI				
SATI-T	48.25± 7.02	32.58± 4.85	8.07	<.0001
SATI-S				
Pre-scanning	41.35± 8.31	31.05± 4.72	4.73	<.0001
Post-scanning	37.65± 9.54	32.68± 7.02	1.84	.073
Head motion				
Translation (mm)	.03± .01	.04± .02	−1.15	.259
Rotation (°)	.03± .01	.03± .02	−.95	.351

Data from questionnaires are presented in terms of mean score (M) and standard deviation (SD) in SAD and HC groups. Statistical comparisons between the two groups are also provided.
SAD, social anxiety disorder; HC, healthy controls; LSAS, Liebowitz Social Anxiety Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; STAI, State-Trait Anxiety Inventory.
[a] The *p* value was obtained by Kruskal–Wallis test. The other *p* values were obtained by two-sample two-tailed *t*-test.

The present study was approved by the local Ethics Committee of Huaxi Hospital, Sichuan University, and a written informed consent was obtained from all subjects.

Image acquisition

Experiments were performed on a 3.0-T GE-Signa MRI scanner (EXCITE, General Electric, Milwaukee, USA) in Huaxi MR Research Center. Foam padding was used to minimize head motion for all subjects. Functional images were acquired using a single-shot, gradient-recalled echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms and flip angle = 90°). Thirty transverse slices (FOV = 24 cm, in-plane matrix = 64 × 64, slice thickness = 5 mm, without gap, voxel size = 3.75 × 3.75 × 5), aligned along the anterior commissure–posterior commissure (AC–PC) line were acquired. For each subject, a total of 205 volumes were acquired, resulting in a total scan time of 410s. Subjects were instructed simply to rest with their eyes closed, not to think of anything in particular, and not to fall asleep. Subsequently, for spatial normalization and localization, a set of high-resolution T1-weighted anatomical images was acquired in axial orientation using a 3D spoiled gradient-recalled (SPGR) sequence (TR = 8.5 ms, TE = 3.4 ms, flip angle = 12°, matrix