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Regional homogeneity changes in social anxiety disorder: A resting-state fMRI study

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ABSTRACT

The previous task-based or resting perfusion studies in social anxiety disorder (SAD) patients have highlighted specific differences in brain response. Little is known about the changes in the local synchronization of spontaneous functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) signals that occur in SAD during the resting state. We investigated altered neural activity in the resting state using a regional homogeneity (ReHo) analysis on 20 SAD and 20 healthy controls (HC). Compared with HC, SAD patients exhibited decreased coherence (ReHo) in the bilateral angular gyrus and the left medial prefrontal cortex within the default mode network (DMN), suggesting functional impairment of the perception of socially relevant emotional state and self-related mental representations; and also in the right dorsolateral prefrontal cortex and right inferior parietal gyrus within the central-executive network (CEN), reflecting the deficit of cognitive control of social anxiety. Significantly increased coherence (ReHo) was found in the left middle occipital gyrus, which would be consistent with their hypervigilance and hyperprosexia to the social communication even in the resting state. Our results might supply a novel way to look into neuro-pathophysiological mechanisms in SAD patients.

1. Introduction

Social anxiety disorder (SAD) is a common and chronic mental disorder (Stein and Stein, 2008), which is thought to involve emotional hyperactivity, cognitive distortions, and ineffective emotion regulation (Goldin et al., 2009b). Results of neurophysiological and neuroimaging studies (Damsa et al., 2009; Engel et al., 2009) showed that patients with SAD exhibited greater activity than healthy subjects in several brain regions related to emotional processing under social fear and anxiety conditions (Tillfors et al., 2001; Stein et al., 2002; Phan et al., 2006; Etkin and Wager, 2007). However, these studies were performed under task-based conditions. Further understanding of SAD may be achieved during the resting state (Etkin et al., 2009), which may be absent or masked during an activation paradigm (Warwick et al., 2008).

Recently, resting-state functional magnetic resonance imaging (fMRI) techniques have been applied to demonstrate abnormalities in various neuropsychiatric disorders (Anand et al., 2005; Garrity et al., 2007; Greicius et al., 2007; Zhang et al., 2009a, 2009b; Liao et al., 2010a, 2010b; Zhang et al., 2010). In particular, these abnormalities mostly relate to alterations in the coherent intrinsic neuronal activity of blood oxygen level-dependent (BOLD) fluctuations observed in resting-state fMRI studies. In a previous study, reduced deactivation of the medial prefrontal cortex (MPFC) and increased deactivation of the posterior cingulate cortex (PCC) were observed in anxiety patients during listening to threatening words as compared to a resting condition (Zhao et al., 2007). These two brain regions are known to be critical in the default mode network (DMN) (Buckner et al., 2008; Broyd et al., 2009). In addition, the results of fMRI and single photon emission computed tomography studies consistently implicate alterations in critical regions in the DMN in SAD patients (Warwick et al., 2008; Gentili et al., 2009). More recently, a pioneering resting-state study showed increased connectivity of a frontoparietal network (the central-executive network (CEN)) and decreased connectivity of an insula-cingulate network (the salience network) in generalized anxiety disorder (Etkin et al., 2009) using functional connectivity analysis. Moreover, our previous study indicated a diffuse impact on widely distributed resting-state networks and selective changes of intrinsic functional connectivity in SAD patients at rest (Liao et al., 2010a).

Regional homogeneity (ReHo), a novel method that differs from functional connectivity, has been developed to analyze the local synchronization of spontaneous fMRI BOLD signals (Zang et al., 2004). The ReHo method assumes that the hemodynamic characteristics of every voxel are similar within a functional cluster and that there is dynamic synchronization of voxels within a given cluster (Zang et al., 2004). ReHo may be absent or masked during an activation paradigm and therefore is useful for resting-state fMRI data analysis. In addition, ReHo provides an approach for using fMRI to investigate local connectivity (Zang et al., 2004) and reflects the temporal synchrony of the regional

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fMRI BOLD signal. It may be potentially helpful to understand human brain activity in the resting state and may be useful for revealing the complexity of human brain function (Liu et al., 2008). In contrast, abnormal ReHo is most likely related to changes in the temporal aspects of spontaneous neural activity in the regional brain (Wu et al., 2009; Shukla et al., 2010). It may be speculated that an abnormal ReHo may be a clue to disrupted local functionality (He et al., 2007) and may provide insight into the pathophysiology of psychiatric disorder (Liu et al., 2010). This method has been used to investigate the functional modulations and characterize the pathophysiological changes in the resting state in patients with attention-deficit/hyperactivity disorder (Zhu et al., 2008), Alzheimer's disease (He et al., 2007; Liu et al., 2008), depression (Liu et al., 2010; Wu et al., 2010), Parkinson's disease (Wu et al., 2009) and autism spectrum disorders (Paakki et al., 2010; Shukla et al., 2010).

Little is known about the changes in the local synchronization of spontaneous fMRI BOLD signals that occur in SAD during the resting state. We hypothesized that ReHo of resting-state brain activity would be different between patients with SAD and healthy controls, particularly in brain regions that have been implicated in previous task-based fMRI studies. In the present study, we document for the first time the ReHo values for patients with SAD compared to those of HCs. In addition, correlation analyses of the ReHo value for each voxel within one-sample *t*-test results were carried out in the SAD group to explore whether changes are related to clinical severity as measured by the total Liebowitz Social Anxiety Scale (LSAS).

2. Methods

2.1. Participants

The present study was approved by the local Ethics Committee of Huaxi Hospital, Sichuan University, and written informed consents were obtained from all subjects. These subjects have been used in our previous study (Liao et al., 2010a), in which the details of subjects' information were described. A first study group was composed of 20 patients (22.90 ± 2.99 years, all right-handed). Diagnosis of SAD was determined by consensus between the two attending psychiatrists and a trained interviewer using the Structured Clinical Interview for DSM-IV (SCID)-Patient Version. SAD patients did not receive psychotherapy and psychiatric medications. A second group, which was composed of 20 age-, sex-, and education-matched healthy controls (HC) (21.65 ± 3.57 years, all right-handed), was recruited and screened using the SCID-Patient Version to confirm the current absence of psychiatric and neurological illness. All participants of the two groups were evaluated with the Liebowitz Social Anxiety Scale (LSAS), Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1988), Hamilton Anxiety Rating Scale (HAMA), and Hamilton Depression Rating Scale (HAMD). More specifically, the STAI questionnaire consists of two components: the STAI-S score, which gives the level of state anxiety at the time of completing the text and the STAI-T score, which measures the inherent trait anxiety level of the subject. The STAI-T questionnaire was measured immediately before and after the MRI scanning (pre-scanning and post-scanning) session (Campbell et al., 2007).

2.2. Image acquisition

Experiments were performed on a 3.0-T GE-Signa MRI scanner (EXCITE, General Electric, Milwaukee, USA) in Huaxi MR Research Center. 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 and the first five volumes were discarded to ensure steady-state longitudinal magnetization. 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 size = 512 × 512 × 156 and voxel size = 0.47 × 0.47 × 1 mm^3) on each subject.

2.3. Data preprocessing

Data preprocessing was carried out using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). The 200 volumes were first corrected for the temporal difference and head motion. One data set was excluded from the analysis because the translational or rotational parameters in a data set exceeded ±1.5 mm or ±1.5°. The functional images were realigned with the corresponding T1-volume and warped into a standard stereotaxic space at a resolution of 3 × 3 × 3 mm^3, using the Montreal Neurological Institute (MNI) echo-planar imaging template in SPM8. Data were temporal band-pass filtered ($0.01 < f < 0.08$ Hz) to reduce the effects of low-frequency drift and physiological high-frequency noise (Biswal et al., 1995), and the linear trend was removed.

2.4. ReHo analysis

We used Kendall's coefficient of concordance (KCC) (Kendall and Gibbons, 1990) to measure the similarity of the time series within a functional cluster based on the regional homogeneity hypothesis (Zang et al., 2004). In the current study, 27 nearest neighboring voxels were defined as a cluster and a KCC value was given to the voxel at the center of this cluster (Zang et al., 2004) as follows:

$$W = \frac{\sum (R_i)^2 - n(\overline{R})^2}{\frac{1}{12}K^2\left(n^3 - n\right)}$$

where W is the KCC among given voxels, ranging from 0 to 1; R_i is the sum rank of the ith time point; $\overline{R} = (n+1)K/2$ is the mean of the R_is; K is the number of time series within a measured cluster; n is the number of ranks (here, $n = 200$ time points). The individual ReHo map was generated in a voxel-wise fashion with the free REST software (Resting state fMRI data analysis toolkit, http://sourceforge.net/projects/resting-fmri). Then a mask (made from the MNI template to assure matching with the normalization step), in the REST software, was used to remove non-brain tissue, and for standardization purposes, the individual ReHo map was divided by its own mean KCC value within the mask (Wu et al., 2009, 2010). Finally, the ReHo maps were spatially smoothed with a Gaussian filter of 4 mm of full width at half maximum (FWHM).

2.5. Second-level analysis

One-sample *t*-tests were performed within each group to show where in the brain the standardized KCC value was larger than one. The significant threshold was set at $P<0.05$ (multiple comparison using the false discovery rate (FDR) criterion (Genovese et al., 2002)).

Then, second-level random effect two-sample *t*-tests were performed to compare the ReHo results between the SAD patients and HC subjects within a mask. This mask was created by combining the voxels in both the SAD and HC groups, which were obtained from one-sample *t*-test results. The *t*-map was set at a threshold of $P<0.05$ (combined height threshold $P<0.01$ and a minimum cluster size of 13 voxels), using the AlphaSim program in the REST software, which applied Monte Carlo simulation to calculate the probability of false positive detection by taking into consideration both the individual voxel probability thresholding and cluster size.