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Decreased regional homogeneity in lingual gyrus, increased regional homogeneity in cuneus and correlations with panic symptom severity of first-episode, medication-naïve and late-onset panic disorder patients

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ABSTRACT

This study was designed to explore regional homogeneity (ReHo), an indicator of the synchronization of brain function, in first-episode, medication-naïve and late-onset patients with panic disorder (PD). Participants comprised 30 patients and 21 healthy controls who underwent with 3-Tesla magnetic resonance imaging (MRI) scanning and ReHo functional MRI analysis. All participants were studied with clinical rating scales to assess the severity of PD symptoms. ReHo values were obtained using the REST toolbox (resting-state functional MRI data analysis toolbox). Differences in demographic data and ReHo values between the two groups were evaluated with the independent two-sample *t*-test function of the Statistical Package for the Social Sciences and REST. There were significant differences in clinical ratings between the two groups. No demographic differences were noted. We found decreased ReHo in the left lingual gyrus and increased ReHo in the right cuneus cortex of patients compared with controls. ReHo values of patients were negatively correlated with PD ratings in the right cuneus. ReHo differences found in the left lingual gyrus and the right cuneus might suggest sensory and inhibitory dysfunction in first-episode, medication-naïve, late-onset patients with PD.

1. Introduction

Panic disorder (PD) is a severe form of anxiety that negatively affects the patient's quality of life (Culpepper, 2004). It is characterized by cardiac, neurological and gastrointestinal symptoms, such as chest tightness, palpitations, dizziness, paresthesia, nausea and abdominal pain (Katon, 1986). Different ages of onset of PD may represent different subtypes of PD. PD patients with early onset (before 20 years old) often have comorbid psychiatric disorders, such as major depressive disorder, social phobia and generalized anxiety disorder. Late-onset (after 20 years old) patients with PD have a lesser propensity toward comorbidity (Katerndahl and Talamantes, 2000; Ramsawh et al., 2011). In addition, the late-onset group seems to have different genetic patterns and different degrees of genetic complexity when compared with the early-onset group (Schumacher et al., 2011). The cited studies suggest that the late-onset population might have distinctive clinical and biological features.

Resting-state functional magnetic resonance imaging (RFMRI) examines default patterns of brain activity that are not associated with the performance of any particular task. This imaging approach has seldom been applied in PD. An indicator of RFMRI, regional homogeneity (ReHo), measures similarities of several time series from signals of RFMRI. Relatively few studies have used ReHo analyses to purify a given cluster in task-state FMRI and examine similarities of a given voxel to the nearest neighbor voxels in a voxel-wise way. ReHo represents the synchronizing abilities of neuronal activations in a specific region and is a complementary tool to understand the regional stability of the brain (Zang et al., 2004). Examinations of ReHo have been reported in several neuropsychiatric disorders, such as Parkinson's disease (Wu et al., 2009) and depression (Yao et al., 2009). PD is associated with decreased cerebral blood flow, decreased brain metabolism (Ohta et al., 2008) or vasoconstriction during the occurrence of panic attacks (Marchand et al., 2009). Therefore, ReHo analyses of RFMRI might be helpful in elucidating the brain neurophysiology of PD.

The fear circuitry theory of PD includes several regions, such as the amygdala, anterior cingulate cortex, insula, hippocampus, hypothalamus, brainstem, thalamus and other sensory-related regions (Gorman et al., 2000). Sensory-related regions are connected with the fear circuitry presumed to be involved in processing

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unknown fear and in generating panic attacks. Among these sensory-related regions, the visual association cortex might be an important component of the fear circuitry. This area influences visual identification, attention, perception, recognition memory, interoceptive sensory information processing, and visuospatial transformation (Taylor et al., 1998; Jackson et al., 2006; Kitada et al., 2010), which might be impaired in PD (Uchida et al., 2008). Spoormaker et al. (2010) also found that shock-related fear induced changes in the activity of the bilateral lingual gyrus in subjects with panic-like responses. In addition, significantly increased amounts of rapid eye movement sleep occurred in these subjects, which may suggest an impaired consolidation of the extinction of fear (Spoormaker et al., 2010). It also corresponded to the link between the amygdala and the visual association cortex in the processing of fearful faces and spatial-related attention (Carlson et al., 2009). The visual association cortex also processes visual imagery and regulates autonomic function, which is involved in panic attacks (Gundel et al., 2003). Brain activity in other parts of the visual association cortex, such as the cuneus, is correlated with sympathetic nervous system activity and processing of the autonomic subdimension (O'Connor et al., 2007; Maihofner et al., 2011). This region also plays a role in the perceptions of bodily expressions, threatening or fear-inducing signals (Kret et al., 2011). In a study of an anticipatory anxiety task, the personality trait of neuroticism was associated with activity in the cuneus (Kumari et al., 2007). Fear, anticipatory anxiety, perception arousal and autonomic dysregulations are core symptoms and presentations of PD. Therefore, the visual association cortex might be a component of the fear circuitry of PD.

In this study, we hypothesized that the visual association cortex would have different patterns of ReHo in first-episode, medication-naïve and late-onset PD patients in comparison with controls. In addition, there might be a correlation between ReHo of the visual association cortex and the clinical severity of PD symptoms.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board, Buddhist Tzu-Chi Hospital Taipei Branch. The selection criteria for patients were as follows: (1) Late-onset PD diagnosis (after 35 years old) and psychiatric diagnoses made on the basis of DSM-IV criteria and the Structured Clinical Interview for DSM-IV; (2) absence of other psychiatric illnesses or medical illnesses; (3) moderate severity of PD with a Clinician Global Impression of Severity score >4, Quick Inventory for Depressive Symptoms-Self-Rating 16-item version (QIDS-SR16) score <9, Hamilton Rating Scale for Depression (HDRS) score <7, Hamilton Rating Scale for Anxiety (HARS) score >22, Panic Disorder Symptom Severity Scale (PDSS) score >15, and panic attacks with full blown symptoms >4 times within the 4 weeks preceding the baseline visit (the HDRS and the QIDS-SR16 rate severity of depressive symptoms; the HARS and the PDSS are used to rate the severity of anxiety and panic symptoms); (4) lack of exposure to cognitive behavioral therapy or other types of psychotherapy; (5) psychotropic medication-naïve; (6) no alcohol and substance abuse or dependence; (7) no past history of claustrophobia or discomfort while undergoing MR scanning; and (8) right-handed. The healthy controls had no psychiatric illnesses or significant medical illnesses according to the Mini-International Neuropsychiatric Interview (MINI). At the time of MR imaging, none of the participants were receiving treatment with psychotropic medications. Handedness was determined by the Edinburgh Inventory (Oldfield, 1971). The enrolled subjects were the same population described in a previous publication (Lai and Wu, 2012).

2.2. Resting-state FMRI data acquisition and pulse sequence

An echo planar imaging (EPI) sequence was acquired in 20 axial slices (TR=2000 ms, TE=40 ms, flip angle=90°, field of view=24 cm; 5-mm thickness and 1-mm gap; the sequence duration was 400 s for each subject, 150 time points were acquired, voxel dimensions=$64\times64\times20$) at baseline visit (3 T Siemens scanner housed at the MR center of National Yang Ming University) in patients and controls. All the patients and controls were requested to close their eyes and to relax, although not to sleep, and to move as little as possible during scanning. All participants reported that they were fully awake during MRI during scanning. We also asked them about details of the entire MR acquisition and tried to exclude any influence of dissociative symptoms (Michal et al., 2007). The participants had good recall of the MRI procedure and answered correctly about details of the scanning session.

2.3. ReHo analysis by REST toolbox

EPI data were preprocessed by Data Processing Assistant and Resting-State FMRI (DPARSF, version 1.4; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China) (Chao-Gan and Yu-Feng, 2010) in the context of Statistical Parametric Mapping 5 (SPM5) on the Matlab platform, which included the removal of the first 10 time points due to possible instability of the initial MRI signal and patients' difficulty in adapting to the scanner environment. The procedure encompassed the 20th slice as the reference slice, realignment, normalization with EPI templates and re-sampling with $3\times3\times3$ mm^3, smoothing by full width at half maximum (FWHM) $4\times4\times4$ kernel, detrending and filtering data with residual signals within 0.008–0.08 Hz to eliminate bias attributable to high-frequency physiological noise and low-frequency drift. As all subjects' head movements were less than 0.5 mm in translation and 1° in rotation, by obtaining the motion time courses of all subjects, it was not necessary to exclude any subjects. Final output data after DPARSF preprocessing were then processed by REST (Resting State FMRI Data Analysis Toolkit, version 1.4; State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China.) (Song et al., 2011) to produce ReHo map image files by using a default mask with a cluster greater than 20 voxels. The ReHo analysis is similar to that performed in previous reports and involves the calculation of Kendall's coefficient to measure ReHo or similarity of ranked time series of a given voxel with its nearest 26 neighboring voxels in a voxel-wise way. Kendall's coefficient value was calculated to this voxel, and an individual Kendall's coefficient map was obtained for each subject. Individual ReHo maps were generated by assigning each voxel a value corresponding to the Kendall's coefficient value of its time series around the nearest voxels. So ReHo analysis is a voxel-wise analysis for Kendall's coefficient of the time series of a given voxel with the 26 nearest neighboring voxels. Kendall's coefficient formula (where W is the KCC among given voxels, ranged from 0 to 1) was as follows:

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

$$\overline{R}=\frac{(n+1)K}{2}$$

R_i is the sum rank of the ith time point; $\overline{R}$ is the mean of the R_is; K is the number of time series within a measured cluster ($K=27$, one given voxel plus the number of its neighbors) and n is the number of ranks.

Then intracranial voxels were extracted to make a mask, which assured the matching of normalization steps and removed noise or non-brain tissue on the ReHo map. Each ReHo map was divided by its own mean ReHo within the mask for the purposes of standardization. The modulated ReHo map image files were then smoothed by a FWHM $4\times4\times4$ Gaussian kernel to reduce the noise and residual differences in gyral anatomy.

We also used the REST correlation analysis function to calculate correlations between the regions of ReHo differences, PDSS scores and HARS scores, in an attempt to validate the importance and function of regions of different ReHo between patients and controls, which might prove valuable in understanding the pathophysiology of PD.

2.4. Statistics

The smoothing ReHo map was used for the following independent two-sample t-test analysis function implemented in the REST toolbox. Subsequent group comparison analysis between patients and controls was performed (second-level random effects model, independent two-sample t-test) under the following statistical criteria (uncorrected $p<0.00005$, cluster>10 voxels (Holtz et al., 2012), volume>135 mm^3, T threshold 4.3207, surface-connected theory). Surface-connected theory means the signal activities were connected through the surface of brain regions and voxels were determined, such that if regional millimeter=4, then voxel size=6. The above statistical analysis also used age and gender as covariates to exclude possible influences of these parameters.

3. Results

3.1. Demographic and clinical data

Participants comprised 30 first-episode drug-naïve patients with PD (13 subjects with agoraphobia; 19 females, 11 males,