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Regional homogeneity and functional connectivity analysis of resting-state magnetic resonance in patients with bipolar II disorder

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Abstract

To explore the characteristics of local brain activity in patients with bipolar depression and its correlation with clinical features.

In accord with the diagnostic and statistical manual of mental disorders-IV of bipolar disorder, 21 patients were enrolled while 21 healthy controls were matched with similar gender, age, level of educations. A 3.0T GE magnetic resonance scanner was used to collect the imaging data, and a 2-sample *t* test was performed. Regional homogeneity (ReHo) method was used to estimate regional activation patterns through indices of localized concordance. ReHo values were compared between groups. Seed-based correlation analysis was used to analyze functional connections.

In the patients' group, ReHo (regional homogeneity) values of resting state functional magnetic resonance imaging data on the right cerebellum 4 and 5 area, cerebellar vermis 6 area, left insula were positively correlated with Hamilton depression scale (HAMD) scores. ReHo values on the left of the triangle of inferior frontal gyrus, right inferior frontal gyrus of orbital region showed negative correlation with HAMD scores. The value of ReHo in the patients' group was positively correlated with the patients' Hamilton anxiety scale score in the right fusiform gyrus, and negative correlation was found in the left insula. The ReHo value of the patients' group was negatively correlated with the patients' Montgomery Asberg depression rating scale score in regions of the midbrain. The value of ReHo in patients' group was significantly reduced in the right central front.

The depression and anxiety severity of bipolar depression patients may be associated with the consistency activity of left insula, right cerebellum, and cerebellar vermis related area, fusiform gyrus. In addition, the ReHo of the midbrain neurons activity may be associated with depression level of patients with bipolar II disorder.

Abbreviations: CSF = cerebrospinal fluid, FC = functional connectivity, HAMA = Hamilton anxiety scale, HAMD-17 = Hamilton depression scale-17 items, MADRS = Montgomery Asberg depression rating scale, ReHo = regional homogeneity, rs-fMRI = resting state-functional magnetic resonance image, WM = white matter.

Keywords: bipolar disorder, magnetic resonance, regional homogeneity

1. Introduction

Bipolar disorder is a chronic and debilitating illness with manic and depressive phases. Bipolar depression is associated with longer illness duration and poorer response to treatment than mania.[1,2] With lifetime prevalence of 2% to 4% across various population groups, bipolar disorder is ranked as the 6th highest contributor to the disability burden globally.[3,4] Functional magnetic resonance imaging (fMRI) is a useful tool to explore the

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potential neural pathological basis of bipolar depression, which could elucidate underlying mechanism and improve clinical management.[5] Regional homogeneity (ReHo) is the time consistency of the blood oxygenation level dependent signal of local brain tissue. Abnormal ReHo signals which are associated with changes in neuronal activity in local brain regions, may be applied to analyze the abnormal brain activities. Increased ReHo can reflect internal consistency and excessive activity of neurons in the local brain region.[6,7] Although the ReHo method cannot directly measure the intensity of the local neuron activity, it can reflect the synchronization of neuronal activity in the local brain region. ReHo can also be a supplementary method to characterize resting-state function connectivity. The resting-state functional connectivity (FC) is a useful approach to relate structural alterations to functional abnormalities in certain brain networks.

2. Method

We recruited 21 Bipolar disorder patients and 21 healthy controls from July 2015 to July 2016, in the Department of Psychiatry, the First Affiliated Hospital, Zhejiang university school of medicine. The study protocol of the research followed the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 659). Written consent was obtained from every participant or his or her parent(s) or legal guardians.

Clinical data of all subjects were collected using a standardized research form. The Structured Clinical Interview for diagnostic and statistical manual of mental disorders-IV was applied for diagnosis. Hamilton anxiety scale (HAMA), Hamilton Depression scale, 17 items (HAMD-17), and Montgomery Asberg depression rating scale (MADRS) were used to assess the severity of symptoms, and the safety of magnetic resonance examination was evaluated by magnetic resonance safety questionnaire.

2.1. Data processing

The resting state functional magnetic resonance imaging (rs-fMRI) data preprocessed using SPM12 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm) and DPABI2.3 (http://rfmri.org/dpabi) tool kits on the Matlab 2014b (Mathworks, Natick, MA) software platform. Data were first converted from the raw digital imaging and communications in medicine format to neuroimaging informatics technology initiative format. The first 10 volumes of the rs-fMRI data were discarded for each participant to ensure steady-state longitudinal magnetization. The remaining 170 volumes were slice-time corrected relative to the middle axial slice to account for the temporal difference in acquisition among different slices, and then were coregistered to the first one to correct for head motion during the scan. None of the given data set exceeded 2 mm translation or 2° rotation. The fMRI data were coregistered to the same subject's high-resolution T1-weighted image using a rigid transformation. The coregistered images were then segmented using diffeomorphic anatomical registration through exponential lie algebra and resulted in gray matter, white matter (WM), and cerebrospinal fluid (CSF). The images were then spatially normalized to the standard stereotaxic coordinates of the Montreal Neurological Institute space using an echo planar imaging template and resampled into a voxel size of $3 \times 3 \times 3\,mm^3$. Then, WM, CSF, and head motion using a Friston 24-parameter model were removed as the nuisance variables. Subsequently, ReHo values were calculated. Next, the data were smoothed with an isotropic Gaussian kernel at a full width and at a half maximum of 6 mm to reduce spatial noise. To remove the effects of low-frequency drift and high-frequency noise, such as respiratory and heart rhythms, we used a temporal band-pass filtering (0.01–0.08 Hz). Finally, FC values were computed.

2.2. The ReHo analysis

Based on the method of Zang et al,[6] linear drift (1inearly detrended) and filter processing was performed for the pre-treated fMRI data. To ensure standardization, the ReHo value of individual element was divided by the mean of the total brain ReHo. Finally, the Gaussian smoothing was used to reduce the space noise and error caused by the space standardization process. In the final spatial image, the corresponding value of each individual element reflected the degree of ReHo of the brain function activity in the region. Seed-based correlation analysis was applied to analyze functional connections. Based on voxel (voxel-wise) method, according to the amplitude of low frequency fluctuation results, the region of interest was selected. To merge the regions of interest with the whole brain, the Pearson correlation analysis was applied to analyze each individual element of time sequence. The correlation coefficient (r value) was the FC between the seed points and other voxels of whole brain.

2.3. The FC analysis

We first located brain regions using a data-driven approach, where ReHo values identified significant difference in functional activities between the patient and healthy control groups. The peak locations were selected as the centers as the spherical seeding area with a radius of 6 mm. We then conducted a whole-brain FC calculation for these seeding areas, and converted the results to zFC values using Fisher Z transformation. Two-sample t test was then performed to detect statistical significances, using an Alphasm correction, with $P < .01$ for single voxels, $P < .05$ for clusters. To check possible interrelationship between the FC values and the patients' clinical data, we extracted the ReHo-based regional of interests and the time series data from the patients, and then performed FC analysis for zFC values. Correlating with HAMA, HAMD and MADRS scores, we obtained the results. All these analyses were accomplished on the SPSS platform.

2.4. Statistical processing

General demographic data analysis was performed by SPSS18.0, where measurement data conformed to normal distribution, the 2-sample t test; counting data was checked by Chi-square; $P < .05$ was considered statistically significant. MRI data set analysis results using REST tool software of Gaussian random (Gaussian random fields) correction (single individual $P < .01$, continuous voxel values, $P < .05$, Montreal neuroscience institute coordinates $Z > 2.326$), which meet adjusted $P < .05$ was defined as statistically significant. Pearson correlation analysis was used to analyze the correlation between HAMA, HAMD-17, and MADRS scores and ReHo values.

3. Result

In comparing the demographic data (Table 1) and rating scale scores between the 2 group, there was no statistical difference

Table 1

Demographic data.

Items	Patients group n = 21	Health control n = 21	t/χ^2	P
Age (yr, $\bar{x} \pm s$)	25.8 ± 10.9	25.5 ± 8.6	.094	.926
Gender (male/female)	7/14	7/14	0	1
Marriage (yes/not)	8/13	8/13	2.053	.358
Education (>12 yr) (%)	76.2	71.4	.161	.77
HAMD (score, $\bar{x} \pm s$)	24.0 ± 5.4	–	–	–
MADRS (score, $\bar{x} \pm s$)	23.1 ± 4.8	–	–	–
HAMA (score, $\bar{x} \pm s$)	23.9 ± 7.6	–	–	–

HAMD = Hamilton depression scale, MADRS = Montgomery Asberg depression rating scale.

between groups in terms of gender, age, and years of education ($P > .05$). The ReHo values of bipolar depression patients were positively correlated with HAMA scores in the right fusiform gyrus and negatively correlated in the left insula. The ReHo of bipolar disorder patients was negatively correlated with MADRS scores in certain regions of the midbrain. In the patients' group, ReHo values were positively correlated with HAMD scores in the right cerebellum 4 and 5 area, cerebellar vermis 6 area, leaf area on the left side of the insula lobe, and negatively correlated in the left side of the triangle of inferior frontal gyrus, right inferior frontal gyrus of orbital region (Fig. 1).

We also found decreased ReHo in the right precentral gyrus of the patient group. Previously, Liu et al[8] found that there was a decrease of ReHo in the left insula lobe of patients with major depressive disorder, but no significant correlation was found between the depression scale scores and ReHo value. Wang et al[9] found a positive correlation between intelligence scale score and regional ReHo (inferior parietal lobules, middle frontal, parahippocampal and inferior temporal gyri, right thalamus, superior frontal and fusiform gyri, and the left superior parietal lobule). There is a suggestion that the insula and the central front are likely to be involved in the cognitive and emotional aspects of bipolar depression.

However, the factors that may affect the functional image of resting state are more complex. For example, the significant difference of ReHo values in the left frontal lobe and occipital cluster was found in patients with bipolar depression.[10] ReHo values of patients with bipolar depression had obvious differences on the left side of the ventral clusters compared to ReHo values of unipolar depression patients. In their study, no definite correlation was found on HAMD-17 scores and sub-scores between bipolar depression and unipolar depression patients. Other studies found reduced ReHo values of the left insula and left cerebellum in patients with treatment resistant depression.[11] These findings also suggest that there may be a cross-linking mechanism between bipolar depression and treatment resistant depression.

4. Discussion

In the present study, the ReHo values in some parts of the midbrain were negatively correlated with the MADRS scores. This may suggest a possible decrease in dopamine neurotransmission in the pathogenesis of bipolar depression. Ashok et al[12] found that both dopamine agonists and antagonists could improve depressive symptoms in bipolar disorder. Further studies could understand the relationship between depressive symptoms severity in bipolar disorder and regional cerebral neurotransmission.[13]

Function connectivity changes are usually associated with dysfunction in cognition, language networks and anomalies in specific brain regions. The paracenter lobe, precuneus, and anterior central gyrus, these distinguished brain regions of both groups were respectively analyzed as the regions of interest. The results showed that the FC between the paracenter lobe and the left insula, the left supplementary motor area, the precuneus and the left insula, the left dorsolateral superior frontal gyrus, the central anterior gyrus and the left insula, the left anterior

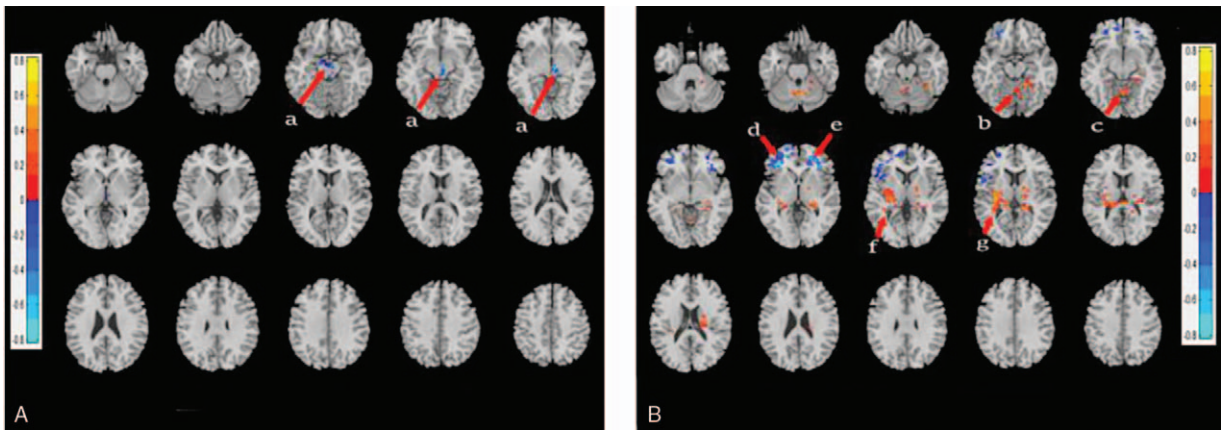

Figure 1. ReHo related with MADRS and HAMD scores. (A) ReHo value was negatively correlated with the MADRS score in the (a) midbrain region. (B) ReHo and HAMD were positively correlated with the (b) right cerebellum 4 and 5; (c) vermis 6; (f) left insula. In the (d) right orbital frontal lobe, (e) the inferior frontal lobe was negatively correlated. HAMD = Hamilton depression scale, MADRS = Montgomery Asberg depression rating scale, ReHo = regional homogeneity.

cingulate and paracingulate gyrus, the left dorsolateral superior frontal gyrus of patients' group were stronger than those in the control group. By merging the distinguished brain regions as regions of interest, our results showed that FC in bipolar depression patient group was more enhanced than the control group, in particular a significant increase in the surrounding area of left middle frontal gyrus and left anterior cingulum. Middle front gyrus and anterior cingulum were known to be responsible for emotion regulation, and the hyper-connectivity of above regions probably may be related to emotional sensitivity of patients with bipolar depression.[14] We also found decreased FC in the surrounding region of right calcarine. Since the frontal and the cingulum play a specific role in cognition, thus these regions may be relevant in cognitive changes in bipolar depression. ReHo analysis found that the frontal lobe ReHo value was positively correlated with HAMD score, pointing to increased FC of left middle frontal gyrus, thus suggesting that frontal lobe may be important in bipolar depression.

The limitations of the study included small sample size. Therefore, further research would require larger sample size and extended follow-up period.

Summarily, our finding indicated that the patients with bipolar II depression have different neural activities compared with healthy control, and may contribute to a better understanding of the potential neural basis of bipolar II disorder.

We will continue to study the functional images of patients with bipolar disorder. Increasing the number of samples will likely result in a change in blood flow in different brain regions, which may help to provide reference to the positioning of a clinical non-drug therapy, such as repeated transcranial magnetic stimulation therapy. The current data were noisy, confounded by other factors, such as age of onset, remittance, duration of onset, and demographic issues. In the future, we will try using more consistent samples so that bias from confounding factors may be minimized.

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