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Research paper

Alterations in regional homogeneity of resting-state brain activity in patients with major depressive disorder screening positive on the 32-item hypomania checklist (HCL-32)

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ABSTRACT

Background: Bipolar disorder (BD) is difficult to diagnose in the early stages of the illness, with the most frequent misdiagnosis being major depressive disorder (MDD). We aimed to use a regional homogeneity (ReHo) approach with resting-state functional magnetic resonance imaging (rs-fMRI) to investigate the features of spontaneous brain activity in MDD patients screening positive on the 32-item Hypomania Checklist (HCL-32).

Methods: Nineteen MDD patients screening positive (HCL-32(+); 9 males; 24.9 ± 5.7 years) and 18 patients screening negative (HCL-32(−); 9 males; 27.1 ± 6.7 years), together with 24 healthy controls (HC; 11 males; 26.4 ± 3.9 years) were studied. ReHo maps were compared and an receiver operating characteristic (ROC) analysis was conducted to confirm the utility of the identified ReHo differences in classifying the patients.

Results: The MDD versus HC showed different ReHo in many brain areas, especially in the frontal and parietal cortex. The HCL-32(+) versus HCL-32(−) showed significant increase of ReHo in the right medial superior frontal cortex, left inferior parietal cortex and middle/inferior temporal cortex, and decrease of ReHo in the left postcentral cortex and cerebellum. ROC analysis showed good sensitivity and specificity for distinguishing these two subgroups of MDD.

Limitations: Recruited patients were all on antidepressants and standard mania rating scales were not performed to assess their hypomanic symptoms.

Conclusions: The rs-fMRI measurement of ReHo in distributed brain regions may be putative biomarkers which could differentiate subthreshold BD from MDD.

1. Introduction

Bipolar disorder (BD) is a common, chronic and complex disease, which can cause psychosocial impairment and has both high mortality and morbidity rates (Angst, 1999; Kemp et al., 2008; Merikangas et al., 2007; Murray and Lopez, 1997). However, it is often difficult to make a correct early diagnosis of BD. Over one third of BD patients may wait 10 years or more before receiving an accurate diagnosis (Hirschfeld et al., 2003). Up to sixty-nine percent of BD patients may be initially misdiagnosed, with the most frequent misdiagnosis being major depressive disorder (MDD) (Hirschfeld et al., 2003). This is undoubtedly partly because a depressive episode is usually the first mood syndrome at the onset of BD and depressive episodes are more frequent than manic/hypomanic episodes (Solomon et al., 2006) (Hirschfeld et al., 2003; Solomon et al., 2006).

MDD patients can be divided into positive (+) and negative (-)

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subgroups according to self-rating screening instruments for BD. The 32-item Hypomania Checklist (HCL-32) has been widely used as a screening instrument for BD in clinical psychiatry in the past decade (Yang et al., 2012; Yang et al., 2011). In the case of HCL-32, MDD patients (identified by the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders; DSM-IV) can be stratified by HCL-32 scores according to the cutoff score between BD and MDD (Angst et al., 2005; Fornaro et al., 2013; Hu et al., 2012). This stratification thus results in one group of patients scoring positive for BD (HCL-32(+)) and another group scoring negative for BD (HCL-32(−)). Some researchers consider HCL-32(+) patients as subthreshold BD patients and HCL-32(−) patients as patients with "true" unipolar MDD (Fornaro et al., 2013; Hu et al., 2012). Follow-up studies have shown that the rates of diagnostic change to full-blown BD are significantly higher in HCL-32(+) patients than the rates in HCL-32(−) patients (Biederman et al., 2014; Holma et al., 2008).

Task-related functional magnetic resonance imaging (fMRI) studies suggest that MDD is associated with abnormalities of a complex series of brain regions (Fitzgerald et al., 2008). The resting-state fMRI (rs-fMRI) is a task-free technique which measures spontaneous brain activities as low-frequency fluctuations in blood oxygen level-dependent (BOLD) signals in the resting brain (Biswal et al., 1995). Instead of focusing on the neural responses under task conditions, rs-fMRI has been utilized to investigate the integration level of neural systems when a non explicit task is engaged (Fox and Raichle, 2007). This rs-fMRI technique has been demonstrated to be a powerful tool which reliably characterizes resting-state brain activities. However, it is important to take into account the abnormalities of neural activities at the baseline state when explaining findings obtained during the task-performing state. Additionally, rs-fMRI is simple and easier operationally compared to task-related fMRI.

The rs-fMRI data analyses includes functional connectivity and voxel-wise metrics of local brain activity. As shown in functional connectivity studies of MDD, affective disorders have been linked to alterations of the default mode network (DMN), the affective network (AN), the salience network (SN), and the cognitive control network (CCN) (Dutta et al., 2014). Thus, it is meaningful to investigate if localized dysfunction of specialized brain regions contributes to network-level abnormalities. Currently, local brain activity information can be assessed by rs-fMRI metrics including regional homogeneity (ReHo), amplitude of low frequency fluctuation (ALFF), fractional amplitude of low-frequency fluctuation (fALFF), voxel-mirrored homotopic connectivity (VMHC) and so on (Zuo and Xing, 2014). ALFF was proposed to measure the intensities of the moment-to-moment low-frequency fluctuations in the fMRI time series (Yu-Feng et al., 2007). ALFF, as well as its normalized version fALFF, is a useful approach with which to map the voxel-wise spatial distribution or regional variation of low-frequency fluctuations across the entire brain. Abnormal baseline ALFF values have been identified in the depressive episode of BD within the prefrontal-limbic network (Liu et al., 2012a, 2012c). We applied an ReHo analysis to processed data in this study. According to one study about the test-retest reliability of voxel-wise rs-fMRI metrics, local functional homogeneity was one of the mostly reliable rs-fMRI metrics (Zuo and Xing, 2014).

The ReHo analysis was originally proposed to measure the degree of signal synchronization of fMRI time-courses (Zang et al., 2004). The hemodynamic characteristics of every voxel within a functional cluster are assumed to be similar and there is a dynamic synchronization of voxels within a cluster. The ReHo method can be used to assess the consistency of a conglomeration of BOLD time series. Therefore, ReHo reflects the temporal homogeneity of the regional BOLD signal, rather than its density and signal intensity (Zang et al., 2004). Abnormal ReHo is considered to be related to changes in the temporal aspects of spontaneous neural activity in the regional brain (Wu et al., 2010). ReHo abnormalities (either increase or decrease in ReHo value) are related to unbalanced local brain activity. In recent years, ReHo has been successfully used to investigate the brain function in healthy subjects (Kunisato et al., 2011; Luo et al., 2014) and clinical populations with psychiatric disorders (Chen et al., 2012; Guo et al., 2011; Liang et al., 2013; Liu et al., 2012d; Zang et al., 2004). For MDD, extensively distributed abnormal brain activities have been observed during resting-state and some clinical symptoms have been related to specific abnormal patterns of brain activities (Yao et al., 2009). Previously, regional ReHo differences have been tested as a differential diagnosis tool of BD and MDD (Liu et al., 2013a). However, it is not clear whether there are differences in brain activity between the two subgroups of MDD patients, i.e., HCL-32(+) patients and HCL-32(−) patients.

In this study, we focused on the whole brain ReHo comparison between these two MDD subgroups. We hypothesized that the HCL-32(+) patients would be different from those HCL-32(−) patients in resting-state brain function and such differences would be captured by the ReHo analysis. If present, any of these differences may be putative biomarker distinguishing HCL-32(+) patients from those patients with "true" MDD.

2. Methods

2.1. Subjects

All patients were recruited from outpatient departments and inpatient units at the department of Psychiatry, Second Xiangya Hospital of Central South University, from April 2012 to June 2013. The inclusion criteria for patients with MDD were: (1) age ≥ 18 and ≤ 60 years and ability to give voluntary informed consent; and that they (2) met the DSM-IV SCID (Structured Clinical Interview for DSM-IV) criteria for MDD and a current major depressive episode (First and Gibbon, 1997; First et al., 2002b); (3) had a total score of 17-item Hamilton Depression Rating Scale (HDRS) ≥ 17 (Hamilton, 1969); (3) satisfied criteria for undergoing magnetic resonance imaging (MRI) scanning based on a screening questionnaire; and (4) had not received electroconvulsive therapy (ECT) in the past four weeks. The diagnoses of MDD were made according to the SCID criteria by two experienced psychiatrists (First and Gibbon, 1997), both of whom had completed a 2-week training program before the diagnostic assessment. The inter-rater reliability of the SCID was tested and yielded satisfactory agreement (Kappa $=0.91$). In total, 43 currently depressed MDD patients were enrolled in this study. The HCL-32, as well as HDRS and Hamilton Anxiety Rating Scale (HAMA) were administered after the patients completed the consent procedure. The HCL-32 is a self-report questionnaire which screens for hypomania (Angst et al., 2005). The multi-lingual hypomania checklist (HCL-32) has been developed and has been widely tested internationally. The Chinese version of HCL-32 has acceptable psychometric reliability and validity in patients with BD (Yang et al., 2008, 2010, 2011, 2012). We used the cutoff of 12, which was the optimal discriminator between MDD and type II BD instead of 14, which was the optimal cutoff between MDD and all BD (Yang et al., 2011, 2012). In China, at the cutoff of 12 between BD and MDD, the sensitivity is 0.86, and the specificity 0.69 (Yang et al., 2011, 2012). The MDD patients with a HCL-32 score higher than or equal to 12 were defined in this study as HCL-32(+) patients, and those with a HCL-32 score lower than 12 as HCL-32(−) patients.

Healthy controls (HC) were recruited by poster or advertisement in local newspapers. Subjects were excluded if they had: (1) a current or past psychiatric diagnosis; (2) organic brain disease; (3) a history of head trauma resulting in loss of