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Research paper

Alteration of cortico-limbic-striatal neural system in major depressive disorder and bipolar disorder

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ABSTRACT

Background: It is often difficult to differentiate major depressive disorder (MDD) and bipolar disorder (BD) merely according to clinical symptoms. Similarities and differences in neural activity between the two disorders remain unclear. In current study, we use amplitude of low-frequency fluctuations (ALFF) to compare neural activation changes between MDD and BD patients.

Methods: One hundred and eighty-three adolescents and young adults (57 MDD, 46 BD and 80 healthy controls, HC) were scanned during resting state. The ALFF for each participant was calculated, and were then compared among all groups using voxel-based analysis.

Results: There was a significant effect of diagnosis in the core regions of cortico-limbic-striatal neural system. Furthermore, MDD showed left-sided abnormal neural activity while BD showed a bilateral abnormality in this neural system.

Limitations: This study was underpowered to consider medications, mood states and neural developmental effects on the neural activation.

Conclusions: Differences in lateralization of ALFF alterations were found. Alterations predominated in the left hemisphere for MDD, whereas alterations were bilateral for BD.

1. Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) share similar depressive symptoms and same diagnostic criteria for depressive episode (Phillips and Kupfer, 2013). Moreover, patients with BD experienced much longer in depressive than manic or hypomanic (Judd et al., 2012) as well as the strict criteria for hypomanic or manic (Phillips and Kupfer, 2013). These are the barriers to distinguish the two diseases. In one large-scale survey study, sixty-nine percent of BD patients had been misdiagnosed with unipolar depression. The misdiagnosed BD patients consulted on average, four physicians before they received a correct diagnosis. Over a third of these patients waited for more than ten years before they received an accurate diagnosis (Hirschfeld et al., 2003). Correctly distinguishing BD from MDD is important, exposing patients with BD to antidepressants may precipitate their first manic episode, increase their rate of mood cycling, and lead to mixed episodes, treatment resistance, and poor prognosis (Berk and Dodd, 2005; Ghaemi et al., 2003; Patel et al., 2015). Misdiagnosis and incorrect medication prescription lead to great pain and economic burden for patients and their families. Above all, it's important to find biomarkers to dissociate MDD from BD in order to prevent the severe consequences of misdiagnosis.

Dysfunction of the cortico-limbic-striatal neural system, including prefrontal cortex (PFC), temporal cortex, the limbic system (including a group of subcortical nuclei and cortical structures such as hippocampus, para-hippocampal gyrus, amygdala and cingulate gyrus) (Waxman, 2013) and striatum has been implicated in both MDD and BD (Kong et al., 2013; Pavuluri and Passarotti, 2008). Several neuroimaging studies have directly compared brain structures and functions between these two populations. Those that have found smaller left-lateralized

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cortical surface area in MDD compared to BD participants (Fung et al., 2015) and greater left-lateralized amygdala BOLD response to sad faces in MDD versus BD (Grotegerd et al., 2014) as well as between-group differences in prefrontal (ACC, ventrolateral PFC, and dorsolateral PFC) network efficiency using independent components analysis (He et al., 2016). Furthermore, a recent study that used a backward-selection support vector machine methods in a sample of MDD and BD participants found that resting state prefrontal activity was able to distinguish the two clinical groups. Above all, cortico-limbic-striatal neural system may be a key to distinguish two diseases. Furthermore, the literatures suggest that in MDD, cortico-limbic-striatal findings are left-lateralized, while they tend to be bilateral in BD. For example, an imaging study employing resting state connectivity methods in treatment-naive MDD patients showed decreased connectivity between the left amygdala and the left ventral PFC (Tang et al., 2013). Adolescent MDD subjects had thicker left caudal anterior cingulate cortex (ACC) and the developmental trajectory of the middle frontal gyrus thickness also shows this left asymmetry in MDD (Reynolds et al., 2014). While there are fewer oligodendroglial and glial cells in the bilateral PFC in BD patients compared to healthy controls (HC) (Rajkowska, 2002; Rajkowska et al., 2001). Meanwhile, previous research conducted by our group has found decreased functional connectivity between the bilateral amygdala and bilateral anterior paralimbic cortices in participants with BD compared to HC while viewing emotional face stimuli (Wang et al., 2012).

Neuroimaging is considered as a promising approach for distinguishing between MDD and BD (Jie et al., 2015; Phillips and Kupfer, 2013). Resting state functional MRI (rs-fMRI) is a non-invasive and advanced neuroimaging measure that detects blood oxygen level-dependent (BOLD) signal during rest to assess brain function. Amplitude of low-frequency fluctuations (ALFF) (Yan et al., 2009; Yang et al., 2007; Zang et al., 2007; Zuo et al., 2010) is an rs-fMRI method which can pinpoint spontaneous neural activity (SNA) of specific brain regional and physiological states. A simultaneous electroencephalography – fMRI study of epilepsy patients found that ALFF may reflect interictal epileptic activity (Zhang et al., 2010). Measuring neuronal activity by means of ALFF may help us to identify distinct locations of brain impairments (Yang et al., 2007). This method has also been widely used to measure intrinsic and regional brain alterations in studies of various mental disorders (Fan et al., 2013; Fryer et al., 2015; Hoptman et al., 2010; Lei et al., 2015; Liu et al., 2016; Y. Liu et al., 2015; Liu et al., 2014; Vargas et al., 2013; Wang et al., 2016; Xu et al., 2014; Zhang et al., 2015), including distinguishing between unipolar depression and BD in depressive state (Jie et al., 2015; Liu et al., 2012). Our group has found altered SNA in MDD and BD using ALFF, suggesting ALFF may be a useful method for the study of mood disorders (Liu et al., 2014; Xu et al., 2014).

In the present study, we compared participants ages thirteen to thirty with either MDD or BD using ALFF. To our knowledge, few studies have directly examined SNA between these two disorders in this age range, which is a critical period of brain development and effective treatment. Based on previous studies and results of our group, we hypothesize that there will be altered SNA of left cortico-limbic-striatal neural system in MDD patients, while BD patients will show bilateral abnormal SNA.

2. Methods

2.1. Subjects

Fifty-seven MDD patients and 46 BD (40 BD-I, 6 BD-II) patients were recruited from the outpatient clinic at the Department of Psychiatry, the First Affiliated Hospital of China Medical University and inpatient department in Mental Health Center of Shenyang. The recruitment interval was from June 2009 to October 2014. The presence of diagnoses and current mood states (elevated mood, depression or euthymia) met criteria via the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), Axis I Disorders (SCID-I, patients' age > 18 years old) (First et al., 2002) or the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL, patients' age ≤ 18 years old) (Kaufman et al., 1997). All the patients were without any other DSM-IV Axis I disorders. Symptom severity was assessed by the 17-item Hamilton Depression Rating Scale (HAMD-17) and Young Mania Rating Scale (YMRS). At the time of scanning , in MDD patients, 51 patients were experiencing a depressive episode and 6 were euthymic. Forty patients were medication-naïve and 17 were treated with psychotropic medications (12 with antidepressant, 1 with antipsychotics, 1 with antipsychotics and antidepressant, 1 with benzodiazepines and zopiclone, 1 with Chinese herbal medication, 1 with zopiclone and Chinese herbal medication), and 53 are right-handed, 1 is left-handed, 2 are mix-handed and 1 is unclear. In BD patients, 10 patients had manic episode, 1 patient had hypomanic episode, 1 was experiencing a mixed episode, 15 were currently experiencing a depressive episode, and 19 were euthymic. Twenty patients were medication-naïve, 26 were prescribed psychotropic medications (13 patients with antipsychotics and mood stabilizer, 2 with mood stabilizer, 1 with antipsychotics, 1 with antipsychotics and antidepressant, 4 with antidepressant and mood stabilizer, 2 with antipsychotics, mood stabilizer and antidepressant, 1 with tandospirone, 1 with antidepressant, 1 with Chinese herbal medication). And 45 are right-handed, 1 is left-handed.

Eighty healthy comparison participants were recruited from the community via advertisements. They were matched by age and gender with the MDD and BD patients and had no personal or familial history of DSM-IV Axis I disorders. In HC group, there are 76 right-handed, 3 are mix-handed and 1 is unclear. Detailed demographic and clinical data of participants is presented in Table 1.

All participants met the following inclusion criteria: 1) aged between 13 and 30 years old; 2) without major medical or neurological illness, hadn't experienced head trauma with a loss of consciousness over 5 min; 3) without MRI contraindication; 4) no substance abuse.

Table 1
Clinical characteristics of HC, MDD and BD subjects.

Variable	HC $n=80$	MDD $n=57$	BD $n=46$	ANOVA		Post Hoc Test, P		
	M (SD, n[a])	M (SD, n[a])	M (SD, n[a])	F/χ^2	P	HC-MDD	HC-BD	MDD-BD
Age (years)	22.40 (4.29, 80)	20.96 (5.15, 57)	22.28 (4.80, 46)	1.73	0.180	0.080	0.893	0.159
Gender male/female	29/51	20/37	19/27	0.47	0.790	–	–	–
Age of First Onset (years)	–	19.63 (5.24, 40)	18.74 (4.80, 43)	–	–	–	–	0.427
Months of Illness	–	14.79 (21.19, 41)	27.91 (32.05, 45)	–	–	–	–	0.027*
HAMD-17 Total	1.15 (1.37, 67)	21.12 (9.17, 57)	10.80 (8.68, 46)	124.83	< 0.001*	< 0.001*	< 0.001*	< 0.001*
HAMA Total	0.58 (1.30, 67)	17.22 (9.77, 46)	7.28 (7.56, 43)	84.83	< 0.001*	< 0.001*	< 0.001*	< 0.001*
YMRS Total	0.06 (0.24, 65)	1.19 (2.40, 47)	10.07 (11.55, 45)	37.01	< 0.001*	0.007*	< 0.001*	< 0.001*

[a] Number of subjects that have this information.
* $P < 0.05$.