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Research report

# Amplitude of low-frequency fluctuations in bipolar disorder: A resting state fMRI study

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ABSTRACT

*Objectives:* The spontaneous low frequency fluctuations (LFF) of blood oxygenation level-dependent (BOLD) signal in resting state have been identified as a biological measure of baseline spontaneous activity in the brain. Increasingly, studies of spontaneous resting state functional connectivity have demonstrated neural network abnormalities in bipolar disorder (BD). This study used the amplitude of low frequency fluctuations (ALFF) to explore the regional functional changes in BD during resting state.
*Methods:* Twenty-nine BD participants and 29 matched healthy controls (HC) were recruited to undergo resting-state functional magnetic resonance imaging scan on a 3.0 T magnetic resonance imaging system. The ALFF of BOLD signal in gray matter for each participant was calculated, and then was compared between BD and HC using ALFF maps.
*Results:* Compared to the HC group, the BD group showed increased ALFF in ventral prefrontal cortex, dorsal lateral prefrontal cortex, frontal eye field, insula, and putamen with extension into the ventral striatum, as well as decreased ALFF in the lingual gyrus ($p < 0.05$, corrected).
*Limitations:* Although we observed differences in ALFF between BD and HC, we cannot conclusively state that these differences are caused by the pathophysiology of BD since most of BD participants were being treated with medications at the time of scanning.
*Conclusions:* Our results revealed altered regional brain activity in BD during resting state. The affected regions have been associated with BD pathophysiology. This suggests that methods using ALFF method may potentially be useful in further studies of this disorder.



## 1. Introduction

Bipolar disorder (BD) is characterized by recurrent and chronic disturbances in mood regulation, sleep, behavior, perception, and cognition, leading to significant disability in affected individuals (Goodwin and Geddes, 2007). Efforts for earlier identification of BD are frequently hampered by the limited objective findings for the disorder. Biomarkers based on brain abnormalities associated with BD could have profound effects in reducing delays in diagnosis of BD.

Functional magnetic resonance imaging (fMRI) has been widely used in the investigation of BD neuropathphysiology. In the past decade, with mounting evidence of task-related fMRI abnormalities, the field has begun to focus on functional abnormalities during resting state. Electroneurophysiological studies have shown that spontaneous neural activity (SNA) is of great physiological importance during resting state (McCormick, 1999) and many brain regions generate their own cyclical patterns that interact with those of other interconnecting regions (Steriade et al., 1993). The spontaneous low frequency (0.01–0.08 Hz) fluctuations (LFF) of blood oxygenation level-dependent (BOLD) in resting state, slower than cardiac or respiratory fluctuations, have been confirmed to indirectly reflect SNA (Cordes et al., 2001; Yang et al., 2007). For example, some investigators have attributed LFF to SNA (Duff et al., 2008; Fox and Raichle, 2007; Fransson, 2006), suggesting that LFF of BOLD signal might be a biomarker for baseline SNA in the brain (Logothetis et al., 2001; Pelled and Goelman, 2004; Rauch et al., 2008).

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Recent studies of spontaneous resting state functional connectivity have focused on the brain network abnormalities in BD. For example, abnormal resting-state functional connectivity in fronto-temporal system (Chepenik et al., 2010; Dickstein et al., 2010) and in corticolimbic system (Anand et al., 2009) has been revealed in both BD children and adults. Chai et al. found abnormal correlations between medial prefrontal cortex and insula, and between medial prefrontal cortex and ventral lateral prefrontal cortex (Chai et al., 2011). These resting state studies in BD have measured functional connectivity using a seed-based method, which focuses on long distance patterns of connectivity. However, it is difficult to pinpoint which specific brain regions are responsible for the observed connectivity alterations. Most recently, amplitude of LFF (ALFF) of BOLD signal, an index to evaluate regional SNA and physiological states of the brain (Mohamed et al., 2004), was used to measure intrinsic and regional brain responses during resting state (Yang et al., 2007; Zang et al., 2007). In this study, we examined differences in ALFF between BD and healthy controls (HC) during resting state.

## 2. Methods

### 2.1. Participants

Twenty-nine participants with BD were recruited from the outpatient clinics at the Department of Psychiatry, First Affiliated Hospital of China Medical University and Mental Health Center of Shenyang. All BD participants were diagnosed by two trained psychiatrists individually using the Structured Clinical Interview for DSM-IV and fulfilling DSM-IV criteria for BD. Twenty-nine HC were recruited from the community of Shengyang, China. HC participants did not have any DSM-IV Axis I disorders in their personal history or their first-degree family members were enrolled. For all participants, mood state at scanning was determined by the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS). Inclusion criteria for study participation were as follows: Participants (1) were between ages 18 and 50, (2) were right -handed, (3) had no history of neurological illness, head trauma with loss of consciousness exceeding 5 min, or major medical condition, (4) had no contraindications for MRI. After a complete description of the study, written informed consent was obtained from all participants in accordance with the Ethics Committee of China Medical University.

At the time of scanning, 5(17.2%) participants with BD met DSM-IV criteria for a depressive episode, 6 (20.7%) for a manic/mixed or hypomanic episode and 18 (62.1%) were euthymic. Detailed demographic and clinical characteristics of the participants are presented in Table 1.

### 2.2. MRI data acquisition

MRI was performed on a GE Signa HDX 3.0 T MRI scanner in the Department of Radiology, the First Affiliated Hospital of China Medical University. Foam pads were used to reduce head motion. Three-dimensional T1-weighted images were acquired in a sagittal orientation employing a Fast Spoiled Gradient-Echo (FSPGR) sequence: repetition time (TR)=7.1 ms, echo time (TE)=3.2 ms, field of view (FOV) =24 cm × 24 cm, flip angle=15°, matrix=240 × 240, slice thickness=1 mm, no gap. Participants were instructed to rest with their eyes closed, relax, and move as little as possible during scanning. Functional images were collected using a gradient echo planar imaging (EPI): TR=2000 ms, TE=30 ms, FOV=24 cm × 24 cm, flip angle=90°, matrix=64 × 64, slice thickness=3 mm, no gap, slices=35.

**Table 1**
Demographic and clinical Data of subjects.

| | Healthy | Bipolar disorder |
|---|---|---|
| *N* | 29 | 29 |
| Age (years, mean ± SD) | 31.38 ± 8.08 | 30.52 ± 8.80 |
| Sex (male:female) | 13:16 | 18:11 |
| HDRS (mean ± SD) | 0.41 ± 0.78 | 9.72 ± 10.14 |
| YMRS (mean ± SD) | 0.06 ± 0.37 | 6.48 ± 9.31 |
| Medication (yes/no) | NA | 24/5 |
| Typical antipsychotics (*N*) | NA | 15 |
| Anticonvulsant (*N*) | NA | 17 |
| Lithium salts (*N*) | NA | 4 |
| Antidepressants (*N*) | NA | 9 |

SD: standard deviation; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; NA=not applicable; *N*=number.

### 2.3. MRI data processing

The imaging data were primarily preprocessed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). For each participant, the first 10 volumes of scanned data were discarded because of magnetic saturation effects, and the remaining images were preprocessed in the following sequential steps: slice timing, motion correction, spatial normalization to the standard Montreal Neurological Institute (MNI) space, and resampling to $3 \times 3 \times 3$ mm$^3$, followed by spatial smoothing with 6-mm full-width at half-maximum (FWHM) Gaussian kernel. Participants with head motion exceeding 2.0 mm in any dimension or 2° of maximum rotation about three axes through the resting-state run were discarded for further analysis. Further data preprocessing and ALFF analysis was performed with Resting-State fMRI Data Analysis Toolkit (REST) (http://www.restfmri.net). Subsequent data preprocessing included removal of linear trends and temporally filtered (band pass, 0.01–0.08 Hz) to remove the effects of very low-frequency drift and high-frequency noise. The calculation procedure was the same as reported in previous studies (Yin et al., 2011). The filtered time series was transformed to a frequency domain with a fast Fourier transform (FFT) (parameters: taper percent=0, FFT length=shortest), and the power spectrum was obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component of the original time series in the time domain, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF (Zang et al., 2007). For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value. The standardized ALFF of each voxel should be a value of about 1, and this standardization procedure is analogous to that used in positron emission tomography studies (Raichle et al., 2001). The global mean ALFF was calculated only within the brain, excluding the background and tissues outside of the brain.

In addition, a gray matter mask was then created by taking the intersections of the normalized T1-weighted high-resolution images of all subjects, which were stripped using the software BrainSuite2 (http://brainsuite.usc.edu). Only the voxels within this mask were further analyzed.

### 2.4. Statistical analyses

For ALFF, a one-sample t-test was performed within each group to determine whether the ALFF differed from the value of 1. A two-sample t-test was performed to see the ALFF difference between the two groups. Voxels with a $P$ value $<0.001$ and cluster size $>297$ mm$^3$ (11 voxels) were considered to show significant difference between the two groups, which was equal to a corrected threshold of $p<0.05$, determined by the Monte Carlo simulation