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Research report

# Altered effective connectivity model in the default mode network between bipolar and unipolar depression based on resting-state fMRI

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ABSTRACT

*Background:* Bipolar depression (BD) is characterized by alternating episodes of depression and mania. Patients who spend the majority of their time in episodes of depression rather than mania are often misdiagnosed with unipolar depression (UD) that only exhibits depressive episodes. It would be important to explore the construction of more objective biomarkers which can be used to more accurately differentiate BD and UD.

*Methods:* The effective connectivity model of BD and UD in the default mode network (DMN) was constructed based on resting-state fMRI data of 17 BD (32.12 ± 8.57 years old) and 17 UD (32.59 ± 9.77 years old) patients using a linear non-Gaussian acyclic model (LiNGAM). The effective connectivity differences were obtained by conducting a permutation test.

*Results:* The following connections were stronger in the BD group than in the UD group: medial prefrontal cortex (MPFC) →posterior cingulate cortex (PCC), right inferior parietal cortex (rIPC)→left hippocampus (lHC) and rIPC→right insula (rInsula). In contrast, the following connections were weak or unapparent in the BD group: MPFC→lHC, rHC→MPFC, rHC→rInsula and rInsula→lHC.

*Limitations:* First, the medication effect is a confounding factor. Second, as with most fMRI studies, the subjects' thoughts during imaging are difficult to control.

*Conclusions:* The brain regions in these altered connections, such as the HC, insula, MPFC and IPC, all play important roles in emotional processing, suggesting that these altered connections may be conducive to better distinguish between BD and UD.



## 1. Introduction

Bipolar depression (BD) is one of the most common and severe mental diseases (de Almeida and Phillips, 2013; Liu et al., 2012; Murray and Lopez, 1996), which can lead to serious damage to the family, occupation and society (Hirschfeld and Vornik, 2005; Yatham et al., 2009). It is characterized by alternating episodes of depression and mania, but patients spend more time in the depressive phase than in the manic phase (Chen et al., 2011; Judd et al., 2003). Thus, BD is often misdiagnosed with unipolar depression (UD) that is characterized by depressive episodes alone (Bowden, 2001; Versace et al., 2010). Frequent misdiagnoses of one of these two conditions to another will lead to inappropriate treatment, high medical costs and poor outcomes (Bowden, 2010; Hirschfeld et al., 2003). Thus, it would be important to explore the construction of more objective biomarkers which can be used to more accurately differentiate BD and UD. Neuroimaging technology such as functional magnetic resonance imaging (fMRI) has been a promising method to investigate neurophysiological and neuroanatomical correlates of affective disease (Hamilton et al., 2011; Strakowski et al., 2014). Applications of fMRI and other imaging technologies may help to reveal the characteristics of BD and UD, or to provide auxiliary for the identification between BD and UD.

Resting-state functional MRI has become a valuable tool for the investigation of brain network function (Biswal et al., 1995; Greicius et al., 2003), and it holds great promise for examining abnormalities in mental disease patients (Hasler and Northoff, 2011). For example, the resting-state functional connectivity of BD and UD was compared, indicating a more severe decreased connectivity in the BD patients than in the UD patients (Anand et al., 2009). Differences in resting-state brain activity between BD and UD patients were investigated by measuring the amplitude of the low-frequency fluctuations (ALFF) of fMRI signals, and the results supported the

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belief that insular sub-regions contribute to the precise differences between BD and UD (Liu et al., 2012). Effective connectivity analysis, focusing on the causal relationship between brain regions, is widely used in the studies of resting state brain networks. It can reflect how one brain region influences another and can quantitatively depict the strength of such influence (Friston, 1994). Studies have shown that the altered effective connectivity may serve as a potential biomarker to reveal characteristics of neurological disease such as Alzheimer's disease (Wu et al., 2011) and primary progressive aphasia (Sonty et al., 2007). Similarly, the application of effective connectivity in the depression studies may reflect more pathophysiological characteristics of depression patients from a new perspective and potential use as a biomarker.

The default mode network (DMN) is a group of areas in the human brain, and some of its regions are most active when people are in a resting state (Raichle et al., 2001; Raichle and Snyder, 2007; Sheline et al., 2009). Studies have found that the DMN is related to reviewing past knowledge for preparing future action (Binder et al., 1999), episodic memory processing (Greicius et al., 2003) and so on. Although the exact function of the DMN is still not clear, a large number of studies have shown that some regions in the DMN are associated with mental diseases, such as BD and UD (Adler et al., 2006; Altshuler et al., 2005; Killgore et al., 2008; Malhi et al., 2007; Peng et al., 2011; Sprengelmeyer et al., 2011; Yurgelun-Todd et al., 2000). However, most of these studies are based on the level of brain activity. Effective connectivity differences between BD and UD in the DMN are yet to be explored.

The current study aimed to identify DMN effective connectivity differences between BD and UD patients. The DMN effective connectivity pattern of these two groups of patients was constructed using resting-state fMRI data by a linear non-Gaussian acyclic model (LiNGAM) (Shimizu et al., 2006). In Shimizu's study, the linear non-Gaussian acyclic model (LiNGAM) was proposed, and a non-Gaussian method closely related to independent component analysis (ICA) called ICA-LiNGAM algorithm was also developed to estimate the new model. Recently, an improved method called pooling-LiNGAM (pLiNAM) was proposed to make the results more stable (Xu et al., 2014). The effective connectivity differences estimated from the pLiNGAM algorithm in the present study may become possible indices for distinguishing BD patients from UD patients.

## 2. Methods

### 2.1. LiNGAM theory

First, the LiNGAM theory based on ICA algorithm (Shimizu et al., 2006) was introduced.

Suppose that there exists a causal order $h(i)$ among variables $x_i (i \in \{1, 2, \ldots, m\})$, in that no later variable determines any earlier variable. The variables $x_i$ are generated recursively (Shimizu and Kano, 2008), and can be represented by a directed acyclic graph (DAG) according to their causal order (Pearl, 2000; Spirtes et al., 2000).

Each variable $x_i$ can be represented by a linear combination of its parent variables:

$$x_i = \sum_{h(j) < h(i)} b_{ij} x_j + e_i + c_i \quad (1)$$

where $b_{ij}$ represents the connection strength from variable $x_j$ to $x_i$, $c_i$ indicates an optional term and $e_i$ denotes a non-Gaussian noise and are independent of each other.

The model (1) can be transformed and rewritten in a matrix form:

$$\mathbf{x} = \mathbf{Bx} + \mathbf{e} \quad (2)$$

where $\mathbf{x}$ is a vector constituted by all the variables $x_i$, $\mathbf{B}$ is the connection strength matrix for the variables, and can be permuted to a strict lower triangular matrix if there exists a causal order of the variables. Eq. (2) can be further written as:

$$\mathbf{x} = \mathbf{Ae} \quad (3)$$

where $\mathbf{A} = (\mathbf{I} - \mathbf{B})^{-1}$. For $\mathbf{B}$ can be transformed to a strict lower triangular matrix, $\mathbf{A}$ can be permuted to lower triangularity (but not strict lower triangularity) with all diagonal elements non-zero. Due to the independence and non-Gaussianity of $\mathbf{e}$, Eq. (3) defines an independent component analysis (ICA) model.

A model with the characteristics above can be called a Linear, Non-Gaussian, Acyclic Model (LiNGAM).

ICA is essentially able to estimate $\mathbf{A}$ (and $\mathbf{W} = \mathbf{A}^{-1} = \mathbf{I} - \mathbf{B}$) if given enough observed vectors $\mathbf{x}$, but it has indeterminacies of permutation, scaling and sign. Actually, ICA gives $\mathbf{W} = \mathbf{PDW}$, where $\mathbf{P}$ is an unknown permutation matrix and $\mathbf{D}$ is an unknown diagonal matrix. In LiNGAM algorithm, since matrix $\mathbf{B}$ can be permuted to a strict lower triangular matrix and $\mathbf{W} = \mathbf{I} - \mathbf{B}$, the correct permutation matrix $\mathbf{P}$ is the only one that gives no zeros in the diagonal of $\mathbf{DW}$ (Shimizu et al., 2006). Then, the correct scaling and signs of the independent components can be found by using the unity on the diagonal of $\mathbf{W} = \mathbf{I} - \mathbf{B}$. The rows of $\mathbf{DW}$ have to be divided by its corresponding diagonal elements to obtain $\mathbf{W}$. Finally, the matrix $\mathbf{B} = \mathbf{I} - \mathbf{W}$ can be computed (Shimizu et al., 2006, 2011).

Previous study on simulated data showed that the ICA-LiNGAM algorithm need more data points (e.g., more than 1000 data points) to perform more stably (Smith et al., 2011). However, the number of data points in most fMRI is usually no more than 300. To solve this problem, an improved method called pooling-LiNGAM (pLiNGAM) was proposed by Xu et al. (2014), and its feasibility and efficiency was demonstrated by the estimation of effective connectivity on both simulated and real fMRI data. The pLiNGAM algorithm obtains long data points by pooling data points across multiple subjects and the pooling subject is called as virtual subject (Smith et al., 2011; Xu et al., 2014). Then the traditional ICA-LiNGAM method is used to estimate the casual relationship models for the virtual subjects. Details about the pLiNGAM algorithm are not included in this research because of concerns about limitations on the paper length. See Xu et al. (2014) for more detailed theory of the pLiNGAM. Considering the stability of the results, the pLiNGAM method was chosen to construct the effective connectivity models of BD and UD.

### 2.2. Subjects

Patients involved in this study were recruited from the outpatient clinic at Anding Hospital, Capital Medical University and included 17 currently depressed individuals with bipolar depression [6 males and 11 females, ages between 20 and 53 years (mean ± SD: 32.12 ± 8.57 years)] and 17 currently depressed individuals with unipolar depression [5 males and 12 females, ages between 21 and 57 years (mean ± SD: 32.59 ± 9.77 years)]. There were no significant differences between the two groups in age, gender, or educational level, and all patients were right-handed. Diagnoses of BD and UD were made based on DSM-IV (The Diagnostic and Statistical Manual of Mental Disorders). Demographic statistics and clinical features of the subjects are shown in Table 1. The study was approved by the Imaging Center for Brain Research, Beijing Normal University and the Institutional Review Board of Anding Hospital, Capital Medical University. In addition, all subjects provided written informed consent prior to entering the study.