Journal of Psychiatric Research 98 (2018) 99–106

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

# Resting-state fMRI signals in offspring of parents with bipolar disorder at the high-risk and ultra-high-risk stages and their relations with cognitive function

Kangguang Lin[a,b,c,d,*,1], Robin Shao[a,c,1], Rui Lu[a], Kun Chen[a,b], Weicong Lu[a,b], Ting Li[a], Jiehua Kong[a], Kwok-Fai So[d,e,f], Guiyun Xu[a,b,**]

[a] Department of Affective Disorders, The Affiliated Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[b] Laboratory of Emotion and Cognition, The Affiliated Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China
[c] Laboratory of Neuropsychology, University of Hong Kong, Hong Kong
[d] Ministry of Education Joint International Research Laboratory of CNS Regeneration, Jinan University, Guangzhou, China
[e] Co-Innovation Center for Neuroregeneration, Nantong University, Nantong, China
[f] The State Key Laboratory of Brain and Cognitive Sciences and Department of Ophthalmology, The University of Hong Kong, Hong Kong

ARTICLE INFO

*Keywords:*
Bipolar disorder
High-risk offspring
Ultra-high-risk offspring
Resting-state fMRI
Limbic network
Cerebellum

ABSTRACT

*Background:* Bipolar disorder (BD) has been associated with dysfunctional resting-state brain functioning. However, it is still not known whether the aberrant functioning occurs and predict cognitive functioning before illness onset.

*Aims:* We examined the resting-state regional and network dysfunctioning, and their correlates with neurocognitive performance, in the high-risk (HR) and ultra-high-risk (UHR) stages of bipolar disorder.

*Methods:* Using amplitude of low-frequency fluctuations (ALFF), region homogeneity (ReHo) and hypothesis-driven region-of-interest (ROI)-based connectivity, we examined resting-state fMRI data of 8- to 25-year-old healthy offspring (HR, n = 28) and offspring with subthreshold syndromes (UHR, n = 22) of a BD parent, and age-matched healthy controls without any personal or family psychopathology (HC, n = 46). Participants' neurocognitive profiles were assessed using the MATRICS Consensus Cognitive Battery (MCCB).

*Results:* ALFF signals in the left putamen and right rolandic operculum were lower in the HR group compared to the HC group. In contrast, ALFF signals were increased in the UHR group in the right middle pars orbitalis of the inferior frontal gyrus, right calcarine sulcus and right cerebellum. Connectivities between the right amygdala and left inferior temporal gyrus, between the left hippocampus and inferior occipital gyrus, and between the left hippocampus and middle pars orbitalis gyrus were decreased in the HR group compared to the HC group. In UHR versus HC group, connectivity between the right amygdala and the left hippocampus and left insula was increased, and connectivity between the left hippocampus and the left insula and the cerebellum was also increased. Among cognitive measures, processing speed was positively correlated with ALFF signals in the left putamen in the HR offspring. In the UHR offspring, processing speed, attention, and verbal learning/memory were positively correlated with the functional connectivity between the left hippocampus and cerebellum.

*Conclusions:* Offspring of parents with BD in the HR and UHR stages show largely non-overlapping patterns of atypical resting-state signals and functional connectivity that predicted cognitive functioning, possibly reflecting inherited abnormalities and/or complimentary reactions.

Bipolar disorder (BD) is a chronic mental illness characterized by recurrent episodes of depression and (hypo)mania, which can lead to great damage to families, businesses and society (Yatham et al., 2009). The worldwide prevalence of bipolar disorder is about 1% (Merikangas et al., 2011). One of the greatest risk factors for BD is a positive family history. Offspring of parents with BD have an increased risk of

* Corresponding author. Department of Affective disorders, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), 36 Mingxin Road, Guangzhou, China.
** Corresponding author. Department of Affective disorders, the Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), 36 Mingxin Road, Guangzhou, China.
*E-mail addresses:* linkangguang@163.com (K. Lin), xuguiyun2908@hotmail.com (G. Xu).
[1] Contributed equally.

https://doi.org/10.1016/j.jpsychires.2018.01.001
Received 30 May 2017; Received in revised form 7 January 2018; Accepted 8 January 2018

developing psychoaffective disorders, especially BD (Birmaher, 2011; Duffy, 2014). Moreover, those with subclinical BD-related symptoms also show elevated risk of developing future full-blown episodes (Duffy, 2014).

Aiming to prevent illness onset and mitigate illness progression, a clinical staging model for psychotic disease was proposed by McGorry and colleagues, who suggested that offspring of psychotic patients with subclinical clinical symptoms are in an "ultra-high risk (UHR) state," which closely predicts future onset of psychosis (McGorry et al., 2009). Analogously, BD can also be divided into successive stages. Individuals with genetic risk but mild or absent subclinical symptoms can be classified as in the high-risk (HR) stage, whereas those with subclinical symptoms can be classified as in the ultra-high-risk (UHR) stage (Scott et al., 2013; Frank et al., 2014). Moreover, processing speed, visual-spatial function, and general function were impaired in the UHR group but intact in the HR population (Lin et al., 2015).

Extensive evidence indicates neurocognitive impairments in BD patients, including general intelligence, attention, problem solving, working memory and long-term memory (Cardenas et al., 2016), which impair the patients' quality of life and adversely impact on disease outcome (Bonnin et al., 2010). Importantly, neurocognitive impairments in executive functioning, verbal memory, verbal fluency and processing speed are also observed in unaffected relatives of BD patients (Bora et al., 2009; Daban et al., 2012; Drysdale et al., 2013; Kim et al., 2015). Recently, our lab recruited BD offspring who were themselves not diagnosed with any psychiatric conditions, and found that processing speed, visual-spatial function, and general function were impaired in the UHR group but intact in the HR population, compared to healthy controls with no BD family history (Lin et al., 2015). However, study is lacking that explicitly investigates the relationship between cognitive deficits and resting-state fMRI dysfunctioning among unaffected BD offspring, although limited existing evidence on psychosis patients indicates that ALFF in the inferior frontal cortex and striatum may predict neurocognitive functioning such as processing speed (He et al., 2013; Sui et al., 2015). Notably, accumulating evidence indicates that the cerebellum contributes to various intrinsic neural networks and participates in diverse cognitive functions, such as executive control, episodic memory, salience and sensorimotor processing (Allen et al., 2005; Habas et al., 2009; Sang et al., 2012). Thus, the functional connectivity between the cerebellum and other limbic and prefrontal regions involved in (episodic) mnemonic, executive functioning, and processing speed such as the hippocampus and the lateral prefrontal cortex (Sehatpour et al., 2010; Monti et al., 2015) may be associated with the neurocognitive profile of HR and UHR individuals.

Neuroimaging studies have generally revealed BD-related dysfunctions across the limbic network, including the amygdala, hippocampus, anterior cingulate cortex, and the ventral prefrontal cortex (Chen et al., 2011). Specifically, BD patients show abnormal resting-state brain functioning, reflected by alterations in 1) amplitudes of low-frequency fluctuations (ALFF) that measures intensities of regional spontaneous brain activity; 2) regional homogeneity (ReHo) that quantifies the degree of between-voxel interconnectedness and 3) functional connectivity (rsFC) patterns that characterizes between-region synchronicity and integrity. For example, past studies showed BD-related increase in ALFF in the putamen (Ford et al., 2013; Xu et al., 2014), ventral prefrontal cortex (Liu et al., 2012a; Xu et al., 2014) and the cerebellum (Liu et al., 2012a), and ALFF decrease in the parahippocampus (Liu et al., 2012a). Also, ReHo increases and decreases were noted in BD patients within the medial and ventral frontal cortex (Liu et al., 2012b; Liang et al., 2013) and the cerebellum (Liang et al., 2013). Moreover, altered rsFC patterns among the corticolimbic and cerebellar networks were consistently observed among BD patients (Anticevic et al., 2013; Mamah et al., 2013). Importantly, corticolimbic, striatal and cerebellar resting-state functional connectivity patterns were also changed among unaffected relatives of BD patients (Meda et al., 2012; Khadka et al., 2013; Roberts et al., 2017), which may represent genetic markers (endophenotypes) (Gottesman and Gould, 2003), compensatory responses (Hajek et al., 2013; Roberts et al., 2016; Wiggins et al., 2017) or resilience (Wiggins et al., 2017). On the other hand, evidence on ALFF or ReHo alterations among unaffected BD HR individuals was relatively limited, inconsistent and negative (Lui et al., 2015; Meda et al., 2015). Notably, studying non-affected BD relatives is advantageous since the results of studies involving BD patients may be confounded by disease-related factors such as co-morbidities, course of disease and medication exposure (Pavuluri et al., 2012).

In the present study, we recruited BD offspring in the HR and UHR phases, along with healthy controls with no BD family history, and measured their resting-state neural activities and functional connectivity patterns. In addition, participants' neurocognitive profiles were assessed using a comprehensive cognitive battery that encompasses, among others, the key executive control, mnemonic, processing speed and sensorimotor functional domains (Burdick et al., 2011). By explicitly assessing the relations between resting-state neural patterns and cognitive performance, we were able to pinpoint the functional significance of the alterations in intrinsic neural patterns in the at-risk groups. Due to the paucity of studies that distinguished between HR and UHR, we did not have solid basis for forming explicit hypotheses about the direction of change of the resting-state measures in those groups relative to controls. As limited evidence indicates reduced corticolimbic and cerebellar grey matter volumes in the HR group compared to controls (Lin et al., 2015; Hanford et al., 2016) which may decrease resting-state activities due to partial volume effects (Drevets et al., 2008), while the grey matter volumes were increased in the UHR group (Lin et al., 2015), we tentatively hypothesized that the ALFF signals in the HR population would be decreased, whereas those in the UHR population might be increased which could reflect neurocompensatory processes (Lin et al., 2015; Roberts et al., 2016). Similarly, due to the lack of existing positive evidence on ReHo differences in bipolar relatives/offspring, we formed only weak hypothesis about ReHo change in the HR or the UHR group. Further, based on the recent meta-analysis on neurophysiological dysfunctioning of BD patients (Chen et al., 2011), and recent empirical evidence on resting-state functional connectivity patterns of BD offspring/relatives showing altered rsFC within inferior frontal cortex, putamen, parahippocampus, hippocampus and amygdala (Meda et al., 2012; Khadka et al., 2013; Roberts et al., 2017), we hypothesized that those circuitries would be altered in the HR and UHR samples compared to controls. Finally, we hypothesized, based on existing evidence, that resting-state activities in the inferior frontal cortex and the striatum would be associated with neurocognitive functioning, in particular speed of processing, while functional connectivity between the cerebellum and the hippocampus and lateral prefrontal cortex would be respectively associated with mnemonic, processing speed and executive performance.

## 1. Methods

### 1.1. Participants

The present neuroimaging data were derived from the Recognition and Early intervention on Prodromal Bipolar Disorder (REI-PBD) project (Lin et al., 2015) (ClinicalTrial.gov Identifier: NCT01863628). This study was approved by the Institutional Review Board of the Guangzhou Brain Hospital. Written informed consents were obtained from all participants (if aged 18 years or above) or their guardian (if aged under 18 years). This was an ongoing longitudinal study. The present data included participants whose resting-state MRI data and neuropsychological data were available. Participants were recruited from the Guangzhou Brain Hospital and volunteers and the community. Offspring of BD patients who had not been diagnosed with any psychiatric disorder were recruited. The diagnosis of BD was based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I).