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Disruptions in resting state functional connectivity in euthymic bipolar patients with insomnia symptoms

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ABSTRACT

Insomnia is prevalent in bipolar disorder (BD) even during periods of euthymic mood. We compared resting state brain activity and cognitive function between euthymic BD with and without insomnia, and secondarily to healthy individuals. BD patients with insomnia symptoms showed a significantly lower functional connectivity within the task-positive network, compared to those without insomnia. They also showed significantly slower cognitive processing speed. These two features of BD with insomnia appeared relatively independent of each other. Preliminary findings suggest that exploration of the mechanisms of sleep disturbance in BD could lead to improved understanding and treatment of inattention in BD.

1. Introduction

Insomnia is prevalent in those with bipolar disorder (BD) and remains during euthymic periods (Harvey et al., 2005). Evidence suggests that sleep deprivation contributes to cognitive deficits, impulsivity, relapse, and quality of life (Harvey et al., 2009). Among those adverse outcomes, cognitive deficits are important for patients' social and vocational functioning. Although the cognitive impairments found in persons with BD are often subtle, improving neuropsychological processing may dramatically improve psychosocial functioning in BD patients. However, the precise brain mechanisms underlying circadian rhythm disturbance and poor sleep in BD remain unclear, and very few studies consider sleep disturbance when interpreting imaging findings (McKenna and Eyler, 2012).

Resting-state functional connectivity (rsFC) measures the temporal correlation of spontaneous blood-oxygen-level-dependent (BOLD) signals between spatially remote brain regions during times when subjects are not performing attention-demanding cognitive tasks. Resting state analyses consistently identify two main networks: the default mode network (DMN), involved in self-referential processes including autobiographical memory; and the task positive network (TPN), involved in attentional control and behavioral response via the salience, dorsal attention, and ventral attention subnetworks. (Fox et al., 2005). Alterations in rsFC have been reported in both BD and insomnia.

Resting-state studies of BD suggest abnormal resting-state network function and connectivity, including aberrant DMN connectivity and mood state-related alterations in DMN and TPN. Ongür et al. (2010) reported that the left parietal cortex, left frontopolar cortex and left fusiform gyrus had significantly more coherence with the DMN network in manic and mixed state BD subjects. Another rsFC study showed a significant difference between euthymic BD and healthy controls (HC) in terms of connectivity between the medial prefrontal cortex and the right dorsolateral prefrontal cortex (Favre et al., 2014). Brady et al. (2017) reported greater rsFC between parietal, occipital, and frontal nodes within the dorsal attention network (DAN), one of the TPN, in mania compared to euthymic BD or HC, and hypoconnectivity between dorsal frontal nodes and the rest of the DMN in euthymic BD patients compared to manic BD subjects and HC. These findings suggest that some rsFC abnormalities in DMN and TPN might be related to BD pathogenesis; whereas, some changes in connectivity may be state-dependent.

Several resting-state functional connectivity studies have sought to determine whether patients with insomnia have connectivity alterations in the DMN or TPN. Li et al. (2014) reported that individuals with insomnia showed decreased functional connectivity within the DMN including the medial prefrontal cortex, the medial temporal lobe and the inferior parietal cortices. These are brain regions mediating attention and arousal. *In addition, a structural connectivity study demonstrated reduced cortical thickness covariance between anterior and posterior regions of the DMN in patients with insomnia compared with good sleepers* (Suh et al., 2016). Moreover, a study evaluating resting state networks in the setting of sleep deprivation found selective reductions in DMN

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functional connectivity and reduced anti-correlation between DMN and TPN (De Havas et al., 2012).

Several studies provide evidence that BD patients show specific cognitive deficits even during asymptomatic phases of illness. They exhibit cognitive impairments in executive function, attention span and verbal memory (Bostock et al., 2017). Executive function and cognitive processing speed, in particular, are closely related to daily functioning and quality of life (Tabares-Seisdedos et al., 2008). Altered connectivity in the TPN network is related to working memory and attention problems (Gordon et al., 2014), and DMN connectivity has also been related to cognitive performance (Anticevic et al., 2012). Therefore, we aimed to investigate whether euthymic BD patients with insomnia would show impairment in processing speed and in executive functions compared with BD patients without insomnia and healthy controls. We also examined if there was a relationship between insomnia-related rsFC alteration and cognitive function in euthymic BD. We hypothesized that intra- and inter-network functional connectivity of the DMN and TPN would be lower in euthymic BD with insomnia; and altered connectivity would underlie cognitive deficits.

2. Methods

The study included 52 subjects: 26 HC participants, 13 BD with no report of insomnia (BD), and 13 BD with insomnia (BD-IN). The study protocol was approved by the institutional review boards of the University of California, San Diego, and the San Diego Veterans Affairs Healthcare System. Patients were recruited both from the VA Hospital and from general community clinics and residences and using online advertisement. HC subjects were recruited by advertisements from the community. Written informed consent was obtained from all participants. All subjects were assessed by a trained rater using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (First, 1997). Patients were stable on medications for at least six weeks and were not currently experiencing a mood episode. Clinical rating scales were administered in our study as follows: Hamilton Depression Rating Scale (HAM-D), Positive and Negative Syndrome Scale (PANSS) and the Young Mania Rating Scale (YMRS).

All patients with BD were subtype I and were euthymic, as determined by HAM-D score < 7 and YMRS score < 6. The HC group was matched on age, gender, and education to 26 bipolar patients by propensity score matching analysis. Participants interested in this study were screened to ensure eligibility based on the following criteria: right-handed, no history of neurological (e.g. stroke), psychiatric, or substance use disorders, and did not have MRI contraindications (e.g. pacemaker or other implanted metallic devices).

Insomnia symptoms were assessed using three items on the HAM-D that evaluate early, middle, and late insomnia. *Patients were placed in the BD-IN group if they endorsed one or more of the insomnia items on HAM-D (Nelson et al., 2006).* All participants were administered the Trail Making Test (TMT) of Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001). A cognitive processing speed score was computed for each participant by averaging the raw scores of the Number Sequencing and Letter Sequencing conditions. Executive functioning was assessed with the Number-Letter Switching subtest, and the raw score was used in analyses.

2.1. Imaging data collection and analyses

Imaging data were acquired using a research-dedicated 3 T General Electric Discovery MR750 MRI scanner with a 32-channel head coil. *A high resolution anatomical T1-weighted MRI image was collected using a fast spoiled gradient echo pulse sequence (TE = 4 ms, FA = 8, TR = 600 ms, field FOV = 256 × 192 mm, 176 1-mm thick sagittal slices, voxel size 1 × 1 × 1 mm).* The resulting images were utilized to localize the functional signal. *Spin-echo field maps were also collected with the following parameters: TE: 90, TR: 10000, FOV: 256, Slice thickness: 4 mm, In-plane resolution: 4 × 4 mm.* The BOLD signal for the resting state connectivity scan was measured with *T2**-weighted echo planar images collected with eyes open (TR = 720 ms, TE 33 ms, FA = 52, FOV 180 × 208 mm, 90 × 104 matrix, 72 oblique axial 2 mm slices, voxel size 2 × 2 × 2 mm).

Raw fMRI data preprocessing was implemented with the National Institute of Health's Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). *Preprocessing of MR images included image reconstruction and correction for field inhomogeneities. Specifically, B_0 distortions were corrected using the reversing gradient method (Chang and Fitzpatrick, 1992; Holland et al., 2010; Morgan et al., 2004), estimating the displacement field from separate spin-echo calibration scans that were adjusted for estimated head motion and applied to the series of gradient-echo images. This was followed by registration and automated motion correction with AFNI's 3dvolreg. The first 10 images were discarded to allow for T1-equilibrium. Images were spatially blurred with a Gaussian kernel full width at half maximum of 3 mm. Linear regression was applied to remove sources of spurious variance in the data. In order to correct for confounds, the following nuisance regressors were included: linear and quadratic trends and six motion parameters estimated during image coregistration. The corrected BOLD time series were then low-pass filtered using a cut-off frequency of 0.08 Hz. Individual subject data were registered to Montreal Neurological Institute template using FSL FLIRT program.* A visual inspection was conducted and remaining data points with excessive motion were rejected; *these censored timepoints were not included in calculation of seed-to-seed correlations.*

Time series within each of the DMN and TPN seeds were extracted and maps of voxel-wise correlations to each seed region's time course

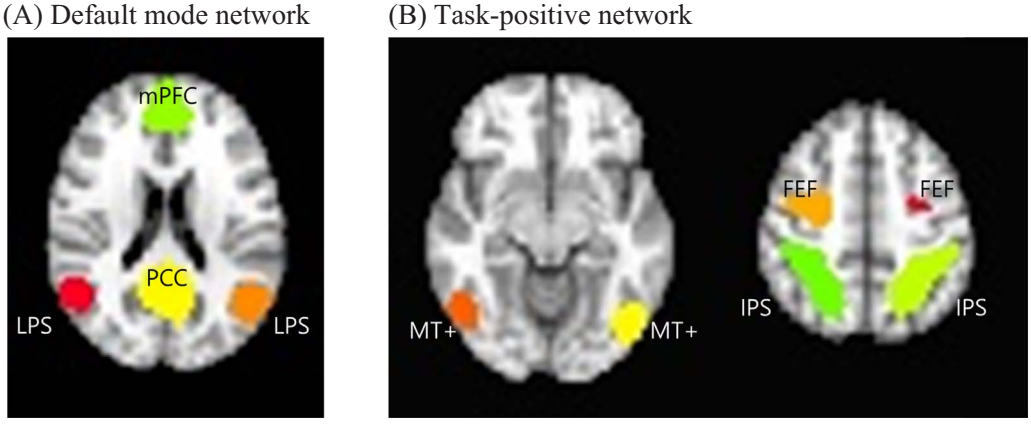

Fig. 1. Regions of interest within the default mode network and task positive network. **Note.** FEF = frontal eye field region; IPS = intraparietal sulcus; LPS = lateral parietal sulcus; mPFC = medial prefrontal cortex; MT+ , middle temporal region. PCC = posterior cingulate cortex. (A) Default mode network(B) Task-positive network.