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Disrupted brain network topology in chronic insomnia disorder: A resting-state fMRI study

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ABSTRACT

This study investigated the topological characteristics of brain functional networks in chronic insomnia disorder (CID) patients. The resting-state functional magnetic resonance imaging and graph theory analysis method were applied to investigate the brain functional connectome patterns among 45 CID patients and 32 healthy controls. The brain functional connectome was constructed by thresholding partial correlation matrices of 90 brain regions from an automated anatomical labeling atlas. The topologic properties of brain functional connectomes at both global and nodal levels were tested. The CID patients had decreased number of module (p = .014) and hierarchy (p = .038), and increased assortativity (p = .035). Furthermore, some brain regions located in the default mode network, dorsal attention network, and sensory-motor network in these patients showed altered nodal centralities. Within these areas, the node betweenness of right central paracentral lobule had positive correlation with the Pittsburgh Sleep Quality Index score (R = 0.319, p = .039). The results imply that functional disruptions of CID patients may be related to disruptions in global and regional topological organization of the brain functional connectome, and provide new and important insights to understand the pathophysiological mechanisms of CID.

1. Introduction

Chronic insomnia disorder (CID) is considered a major public health problem worldwide and is characterized by difficulties in falling asleep at bedtime, frequent awakenings in the middle of the night, and waking up too early in the morning (Spiegelhalder et al., 2015; Kay and Buysse, 2017). Persistent insomnia symptoms will not only reduce the quality of daily life and affect work efficiency but also lead to mental symptoms such as depression and anxiety, and that might become even life-threatening (Li et al., 2016). Several models have been proposed to address the cognitive, physiological, and neurobiological features of CID (Kay and Buysse, 2017). Most study results are interpreted from the perspective of a "hyperarousal" model. However, numerous neuroimaging studies have failed to fully replicate or find any evidence of physiological hyperarousal in patients with CID (Kay and Buysse, 2017). The underlying neural mechanisms remain largely unknown and have attracted much attention (Spiegelhalder et al., 2015; Kay and Buysse, 2017).

Multiple functional neuroimaging based on the blood-oxygen-level dependent (BOLD) effect have been used to improve our understanding of the neural mechanisms of CID (Spiegelhalder et al., 2015; Kay and Buysse, 2017). By applying task-based functional magnetic resonance imaging (fMRI), Altena et al. found that patients with CID had lower activity at the left medial frontal gyrus (MFG) and inferior frontal gyrus (IFG) than healthy controls (HCs) during executive control paradigms (i.e., letter and category fluency) (Altena et al., 2008). Another task-based fMRI study reported that patients with CID showed abnormal activation in amygdala to different stimuli, such as non-insomnia-related stimuli, emotionally arousing stimuli and insomnia-related stimuli (Baglioni et al., 2014). Resting-state fMRI (rsfMRI) refers to the brain state in the absence of explicit input or output (Biswal et al., 1995; Fox and Raichle, 2007; Lee et al., 2013), and has been widely used to understand the neural mechanism of neurological and psychiatric disorders, such as CID, depression, and schizophrenia (Kaiser et al., 2015; Kühn and Gallinat, 2013). Different methods have been applied to find

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the disruptions in the brain activity in CID using rsfMRI, including regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and functional connectivity (FC) (Wang et al., 2016a; Liu et al., 2016; Marques et al., 2017). Some other studies have found disrupted resting-state FC using seed-based region-to-region FC, such as in the amygdala, insula, posterior cingulate cortex, and hippocampus (Huang et al., 2012; Wang et al., 2017). Li and Pang et al. divided the brain into 116 regions and identified abnormal FCs by comparing the Pearson's correlation coefficients of each pair, and their results indicated aberrant FCs in widely distributed regions (Li et al., 2017; Pang et al., 2017). Many previous findings in fMRI described above were focused on the dysfunctions of the circumscribed brain regions or FC changes between two different brain regions. However, the brain is a complex and advanced information processing system that coordinates different brain regions as a functional network (Lehrer, 2009; Xia and He, 2017). Studies have demonstrated that the altered functions of patients with CID, such as cognition performance, emotion processing, and memory formation, are related to widely distributed brain regions and subnetworks (Kay and Buysse, 2017). Therefore, it is necessary to study the neural mechanisms of CID from a functional network perspective.

Recent advances in graph-based rsfMRI analysis methods have facilitated the noninvasive characterization of the brain network during resting-state (Xia and He, 2017). This process proved to be a very effective and informative way to explore brain function and human behavior (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011). In graph theory, the brain network is abstractly defined as a set of nodes (denoting anatomical regions) and interconnecting edges (denoting functional or structural connections) (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011). Topological properties of these graphs can be quantitatively measured with advanced methodologies (Xia and He, 2017). Numerous studies showed that human brain networks have many special topological properties, such as small-world (an optimal brain network organization characterized by high efficiency of information transfer at a low cost) and modularity (an optimal partition of a brain network into smaller functional communities of modules) (Zhang et al., 2011a; Suo et al., 2015). Notably, graph theoretical analysis can be adopted to investigate the functional changes at both global and nodal levels. Such organizational pattern is disrupted in neuropsychiatric disorders, such as major depressive disorder; post-traumatic stress disorder, and schizophrenia (Zhang et al., 2011a; Suo et al., 2015; Liu et al., 2008). However, the topological characteristics of the brain functional connectome in CID remain unknown.

Given the previous evidence of abnormal regional activities and FCs in widely distributed regions, together with the findings of disrupted brain function, we hypothesized that CID may be associated with altered topological organization of the brain functional connectome, such as small-world, modularity, assortativity, hierarchy, and node centralities. In the present study, we testified our hypothesis by employing rsfMRI and graph theoretical analyses to explore into the differences of brain functional connectome between CID patients and HCs. The relationships between group differences and individual clinical variables were further investigated.

2. Materials and methods

2.1. Participants

This study was approved by the Ethics Committee of People's Hospital of Zhengzhou University. All CID patients were outpatients from the neurology department of People's Hospital of Zhengzhou University or recruited via advertising, and HCs were all recruited from advertising. The participants were recruited from 2016 January to 2016 December. All participants provided written informed consent to participate in the study and received equal financial compensation. Sleep-related interviews were conducted by a specialized and experienced neurologist and a standardized screening was administered to determine other factors for exclusion, such as sleep-related movement disorders, hypersomnia, parasomnia, or combined somatic and mental disorder. The CID patients were required to meet the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5) diagnostic criteria. All participants underwent a complete physical and neurological examination, standard laboratory tests, and some psychological assessments. These psychological assessments included Pittsburgh Sleep Quality Index (PSQI), Hamilton Depression Scale (HAMD), and Hamilton Anxiety Scale (HAMA). Moreover, CID patients were required not have taken medicine that would influence brain function two weeks before experiment. The inclusion criteria for CID patients were as follows: (Spiegelhalder et al., 2015) duration of insomnia symptoms, such as fatigue, testiness, or cognitive decline, were required no less than three months; (Kay and Buysse, 2017) PSQI score ≥ 8; (Li et al., 2016) no neurological or psychiatric disorders, such as stroke, depression (HAMD ≤ 17), and anxiety (HAMA ≤ 14) (Pang et al., 2017) etc.; (Altena et al., 2008) no other sleep disorders (such as sleep-related movement disorders, hypersomnia, or parasomnia); (Baglioni et al., 2014) right-hand dominance (determined by Chinese Handedness Inventory that suits Chinese people, including 10 test items) and native chinese speakers; (Wang et al., 2012) age 20–60 years; (Biswal et al., 1995) no medication or substance abuse, such as caffeine, nicotine, or alcohol; (Fox and Raichle, 2007) no abnormal signal found by T2-weighted dark-fluid and T1-weighted MR images. HCs were required to meet the following criteria: (Spiegelhalder et al., 2015) no history of sleep disorders: PSQI ≤ 7; (Kay and Buysse, 2017) good sleep quality and no history of work time at day and night alternation; (Li et al., 2016) no neurological or psychiatric disorders, such as stroke, depression (HAMD ≤ 6), and anxiety (HAMA ≤ 6); (Altena et al., 2008) fulfillment of inclusion criteria 5–8 for the CID patients. Finally, a total of 77 subjects were recruited, which included 45 CID patients and 32 HCs matched in sex, age, and education (Table 1).

2.2. Data acquisition

All fMRI data were acquired by a MAGNETOM Prisma 3 T MR scanner (Siemens Healthcare, Erlangen, Germany) with a 64-channel head-neck coil at the Medical Imaging Center of our Hospital. Foam pads were used to minimize head motions and diminish scanner noise. All subjects were instructed to keep their eyes closed and think of nothing in particular or fall asleep during the acquisition. Routine axial T2-weighted dark-fluid and T1-weighted MR images were acquired to exclude brain structural abnormality. Resting-state functional MR data was acquired using a prototype simultaneous multi-slice echo planar imaging (SMS-EPI) sequence with the following parameters: TR = 1500 ms, TE = 30 ms, FOV = 224 mm × 224 mm; matrix size = 112 × 112, slices = 72, slice thickness = 2 mm, flip angle = 60°, and SMS factor = 4.

Table 1
Demographics and clinical characteristics of the subjects.

Variables	CID (n = 45)	HC (n = 32)	*P* value	*t* value
Age (years)	41.4 ± 10.8	38.1 ± 9.9	0.173	1.376
Gender (male/female)	38/7	22/10	0.102	2.678[a]
Education (years)	12.0 ± 4.6	13.3 ± 4.9	0.242	−1.181
PSQI	13.3 ± 2.8	2.4 ± 1.7	< 0.001	19.321
HAMA	9.8 ± 4.1	1.6 ± 1.8	< 0.001	10.414
HAMD	9.4 ± 3.6	0.8 ± 1.2	< 0.001	12.849

Data are presented as mean ± SD. The [a]*p* value was obtained by two-tailed Pearson chi-square test. *P* values were obtained by two-tailed two independent sample *t*-test. Abbreviation: CID, chronic insomnia disorder; HC, healthy control; PSQI, Pittsburgh Sleep Quality Index; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.