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

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; posttraumatic 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.

2.3. Data processing

Image preprocessing was performed using MATLAB toolbox SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and GRETNA (http://www.nitrc.org/projects/gretna/). The first ten volumes were discarded to allow for scanner stabilization. The remaining volumes were slice-timing corrected and realigned to the first volume for head-motion correction. None of the subjects exceeded 1.5 mm or 1.5° for their translation or rotational parameters. Then the images were spatially normalized to the Montreal Neurological Institute 152 template with 3-mm isotropic resolution and smoothed with a Gaussian kernel of $4 \times 4 \times 4\,mm^3$ full-width at half-maximum. No spatial smoothing was applied to avoid introducing artificial local spatial correlation (Zhang et al., 2011b). The images were linearly detrended and temporally bandpass-filtered (0.01–0.08 Hz) to remove low-frequency drift and high-frequency physiological noise. Finally, the white matter signal, cerebrospinal fluid signal, and motion parameters (three translational and three rotational parameters) were regressed out. The global signal was not regressed out in the present data according to previous studies (Murphy and Fox, 2017).

The brain functional connectome was also constructed using GRETNA. First, an automated anatomical labeling (AAL) atlas was used to divide the brain into 90 cortical and subcortical regions of interest, and each region was considered as a network node. Next, the mean time series were calculated for each region, and partial correlations of the mean time series between all pairs of nodes (representing their conditional dependences by excluding the effects of the other 88 regions) were considered as the edges of brain functional connectome. This process resulted in a 90×90 partial correlation matrix for each subject, which was converted into a binary matrix (i.e., adjacency matrix) according to a predefined threshold, where the entry $a_{ij} = 1$ if the absolute partial correlation between regions i and j exceeds the threshold. Otherwise, $a_{ij} = 0$.

The topologic properties of brain functional connectomes at both global and nodal levels were investigated using the GRETNA toolbox. A range of sparsity thresholds from S1 to Sn with an interval of 0.01, where S1 = 0.05, and Sn = 0.4, was applied to address the various number of edges in different individual subjects (Bassett and Bullmore, 2006). The brain functional connectomes were constructed over the whole range of sparsity thresholds. Clustering coefficient C_p quantifies the extent of local interconnectivity or cliquishness of a network. Decreased C_p implies reduced efficiency in local information transmission and processes (Wang et al., 2016b). Furthermore, characteristic path length L_p measures the extent of overall communication efficiency of a network and increased L_p represents a shift toward "regularization" (Suo et al., 2017). Additionally, global efficiency E_{glob} and local efficiency E_{loc} are the measures of network efficiency in transmitting information at the local and global levels, respectively (Suo et al., 2017). Decreased E_{loc} may damage the connections with linked regions, while decreased E_{glob} may impair the ability to combine specialized information from distributed brain regions. The global network parameters including five kinds, namely, small-world, which include the C_p, L_p, normalized clustering coefficient γ, normalized characteristic path length λ, and small-worldness $\sigma = \gamma/\lambda$, network efficiency parameters (including E_{glob} and E_{loc}), modularity, assortativity, and hierarchy (Boccaletti et al., 2006). The regional nodal parameters included nodal degree, nodal efficiency, and nodal betweenness. The area under the curve (AUC) provided a summarized scalar for the topological characterization of brain functional connectomes, that is, independent of a single threshold selection and sensitive to topological alterations in brain disorders (Zhang et al., 2011a; Suo et al., 2015). Thus, the AUC was calculated for each network metric among all the sparsity.

2.4. Statistical analysis

Statistical analysis of demographic and clinical data was performed

using SPSS software version 19.0 (http://www.spss.com; Chicago, IL). Statistical comparisons of topological properties (both the global network parameters and the regional nodal parameters) between CID patients and HCs were performed using nonparametric permutation method (10,000 permutations). The specific pairs of brain regions with altered FC in CID patients were located by identifying the region pairs that exhibited between-group differences in nodal characteristics. Then, network-based statistics (NBS) method (http://www.nitrc.org/projects/nbs/) was performed to locate the connected regions showing significant changes. Specifically, for each subject, the nodes that exhibited significant between-group differences in at least one of the three nodal centralities (node degree, node efficiency, and node betweenness) were chosen, and then a subset of the connections matrix was generated based on these nodes. Then, the NBS method was applied to define a set of suprathreshold links among all connected components. The significance of each component was estimated using the nonparametric permutation method (10,000 permutations). Benjamini Hochberg false discovery rate (FDR) correction method at a significance level of 0.05 was adopted to address multiple comparisons in nodal centralities and functional connectivities. Detailed description can be found in Suo et al. (Suo et al., 2015). After between-group differences had been identified in the topological properties and nodal metrics, the distribution of these metrics and clinical data (PSQI, HAMA, and HAMD scores) were test by Kolmogorov–Smirnov method. The results showed that all data is normal distribution. Thus, the parametric analyses method of partial correlation was chose to examine the relationships between these metrics and clinical data, with age, gender, and education as covariates.

3. Results

3.1. Demographic and clinical comparisons

No significant differences were found in the age, gender, and education between the CID patients and HCs ($p > .05$; Table 1). The CID patients and HCs showed significant differences in PSQI, HAMA, and HAMD ($p < .05$; Table 1).

3.2. Global topological organization of the functional connectome

Both CID patients and HCs showed small-world topology in the brain functional connectome, as depicted by the high C_p ($\gamma > 1$) and similar L_p ($\lambda \approx 1$) compared with matched random networks, which can be unified by a scalar measure σ ($\sigma > 1$) (Boccaletti et al., 2006). However, no significant differences were found in following global topological properties, including small-world and network efficiency. The CID patients, compared with the HC, showed a significantly decreased number of module ($p = .014$, Fig. 1A) and hierarchy ($p = .038$, Fig. 1C). The CID group significantly increased network assortativity ($p = .035$, Fig. 1B).

3.3. Regional topological organization of the functional connectome

The brain regions with significant between-group differences in at least one nodal metric were identified ($p < .01$, uncorrected). Compared with the HC group, the CID patients showed decreased nodal centralities in the left middle frontal orbital (MFGorb), right MFGorb, left opercular IFG, left triangular IFG, and left angular (Table 2). Increased nodal centralities were found in the right middle cingulum gyrus (MCG), right hippocampus, right cuneus, right central paracentral lobule (PCL), and right inferior temporal gyrus (ITG) (Table 2).

3.4. CID-related alterations in functional connectivity

Significantly altered brain network was found in the CID patients ($p < .05$, uncorrected) compared with the HCs. This brain network had
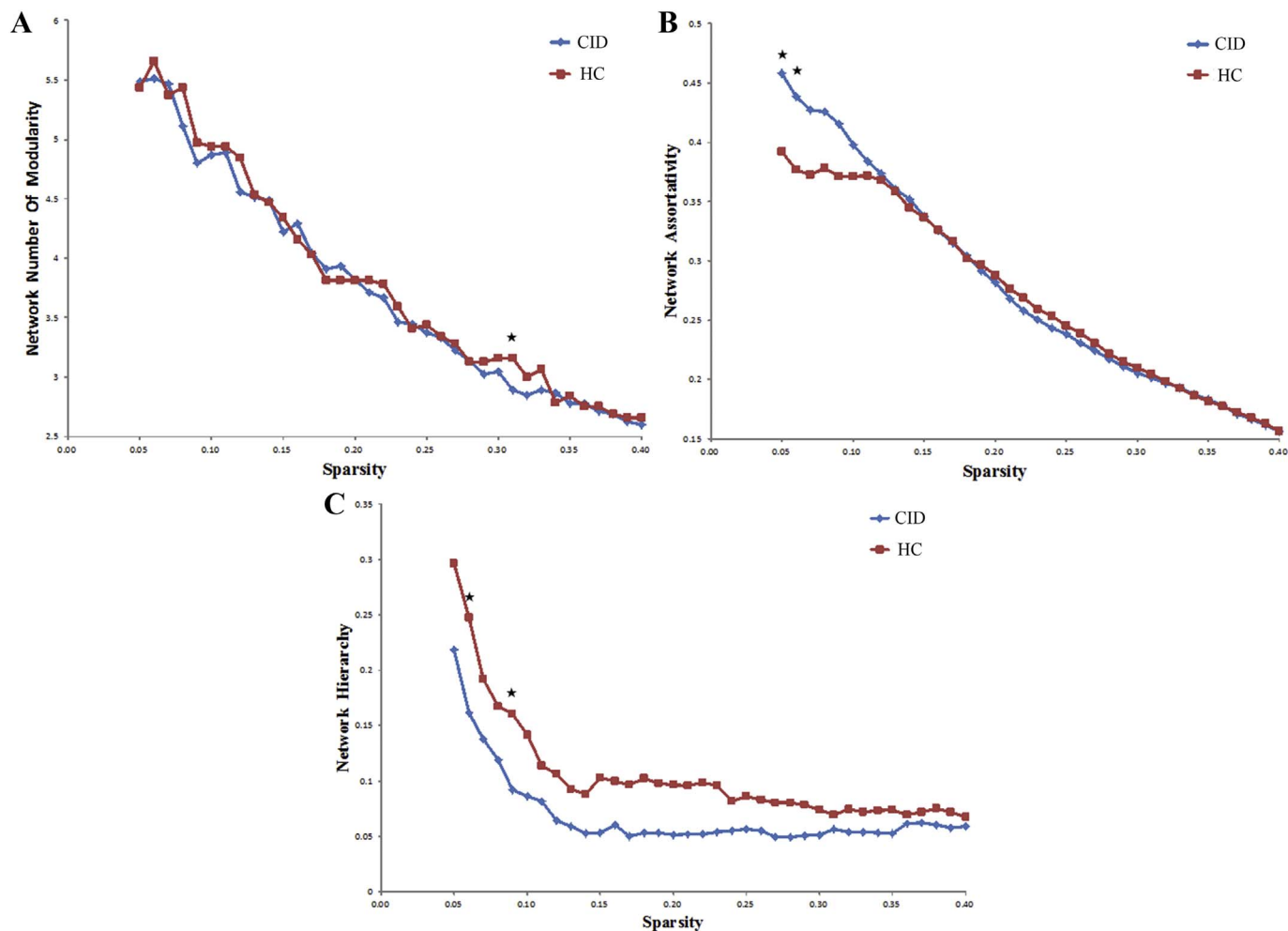
Fig. 1. Altered global topological parameters of the functional connectome across different sparsity thresholds (0.01–0.4). (A) Network number of modularity of the functional connectome. (B) Network assortativity of the functional connectome. (C) Network hierarchy of the functional connectome. Black stars indicate where the difference between CID patients and HCs was significant ($p < .05$). Abbreviation: CID, chronic insomnia disorder; HC, healthy control.

ten nodes and five connections, including three increased and two decreased FCs (Fig. 2, Table 3). The results are visualized using the BrainNet Viewer package (http://www.nitrc.org/projects/bnv).

3.5. Relationships between network metrics and clinical variables

Significant positive correlation was found in the PSQI score with node betweenness of right PCL ($R = 0.319$, $p = .039$; Fig. 3A) but not with the other global network metrics and regional nodal parameters. The node betweenness of right PCL also showed significant positive correlation with the HAMD score ($R = 0.383$, $p = .012$). In addition, negative correlation was observed between HAMD score and network modularity ($p = -0.04$; Fig. 3B). No significant correlation was found in HAMA with the other global network metrics and regional nodal

Table 2
Regions showing disrupted nodal centralities in CID patients compared with HCs (all cost).

Brain regions	*P* value/p_{cor}value		
	Nodal betweenness	**Nodal degree**	**Nodal efficiency**
CID < HC			
Left orbital middle frontal gyrus	**0.0001/0.0050**	**0.0003/0.0265**	**0.0014**/0.1260
Right orbital middle frontal gyrus	**0.0042**/0.2000	**0.0140**/0.5534	**0.0257**/0.4634
Left opercular inferior frontal gyrus	**0.0005/0.0172**	**0.0131**/0.3837	0.0500/0.4992
Left triangular inferior frontal gyrus	**0.0002/0.0168**	**0.0305**/0.4364	**0.0187**/0.2939
Left angular	**0.0044**/0.1085	0.2584/0.4768	0.2644/0.5681
CID > HC			
Right middle cingulum gyrus	**0.0041**/0.1030	**0.0302**/0.4317	**0.0355**/0.4900
Right hippocampus	**< 0.001/ < 0.001**	**0.0003/0.0235**	**0.0016**/0.1336
Right cuneus	0.1421/0.4438	**0.0051**/0.2233	0.0687/0.6107
Right central paracentral lobule	0.0564/0.4763	**0.0107**/0.2397	**0.0034**/0.2074
Right inferior temporal gyrus	**0.0010/0.0320**	**0.0346**/0.4356	**0.0487**/0.4821

P value ($p < .01$, uncorrected); p_{cor} value ($p < .05$, FDR corrected); Regions are considered abnormal in the CID patients if they exhibited significant between-group differences in at least one of the three nodal centralities (shown in bold font). Abbreviation: CID, chronic insomnia disorder; HC, healthy control.
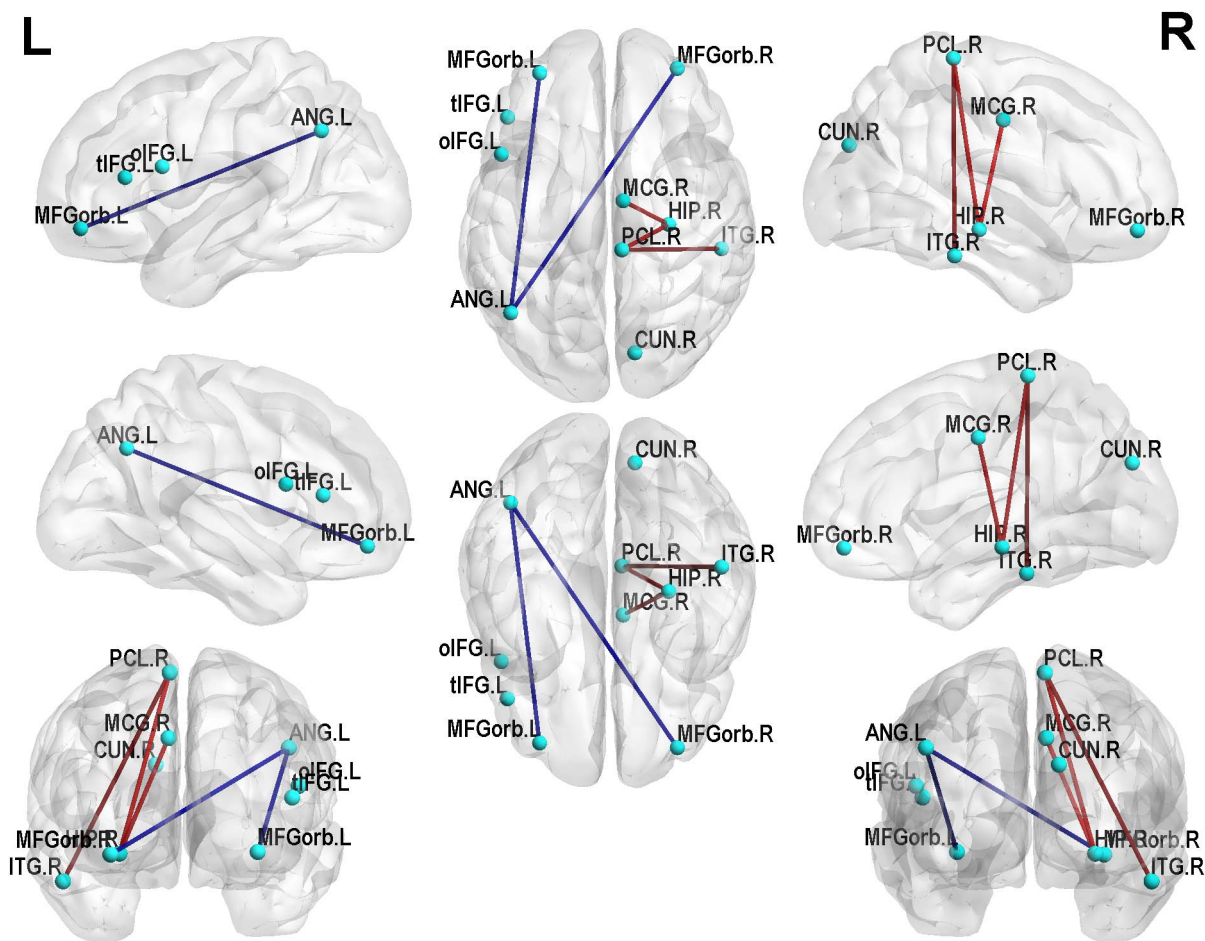
Fig. 2. Significantly altered nodal centralities of the brain functional connectome in CID patients, compared with HCs ($p < .01$, uncorrected). These connections formed a single connected network with ten nodes and five connections ($p < .05$, uncorrected). Red lines represent increased functional connectivity strength in CID patients. Blue lines represent decreased functional connectivity strength in CID patients. Details are listed in Table 3. Abbreviations: MFGorb, middle frontal orbital; oIFG, opercular inferior frontal gyrus; tIFG, triangular inferior frontal gyrus; ANG, angular; MCG, middle cingulum gyrus; HIP, hippocampus; CUN, cuneus; PCL, central paracentral lobule; ITG, inferior temporal gyrus; CID, chronic insomnia disorder; HC, healthy control.

Table 3
Significantly altered functional connectivities in CID patients compared with HCs.

Brain region 1	Brain region 2	P value	t value
Increased			
Right central paracentral lobule	Right hippocampus	0.018	2.42
Right central paracentral lobule	Right inferior temporal gyrus	0.007	2.77
Right middle cingulum gyrus	Right hippocampus	0.022	2.34
Decreased			
Left orbital middle frontal gyrus	Left angular	0.017	− 2.43
Right orbital middle frontal gyrus	Left angular	0.020	− 2.37

P value ($p < .05$, uncorrected); Abbreviation: CID, chronic insomnia disorder; HC, healthy control.

parameters. However, two outliers were found in the node betweenness of right PCL (Fig. 3A). One had the higher PSQI score and highest node betweenness score, the other had the highest PSQI score and lowest node betweenness score. We recalculated the partial correlation with or without the outliers, with age, gender, and education as covariates. The results showed the outliers influenced the significance of the results. However, the node betweenness of right PCL also showed significant correlations with some clinical data (Supplementary Table S1).

4. Discussion

In this study, graph-based theoretical approaches were applied to investigate the topological characteristics of the brain functional connectomes in CID. Compared with HCs, CID patients showed distributed global topological properties and nodal centralities involving multiple specific large-scale brain networks, including the default mode network, dorsal attention network, and sensory-motor network. The node betweenness disruption of right PCL was positively correlated with the severity of insomnia in CID patients. Collectively, these results indicated network architecture and communities in CID patients have changed at the global and nodal level, which provided unequivocal evidence supporting our hypothesis that CID disrupted the topological organization of the brain functional connectome to some extent.

Previous studies have demonstrated that the complex functional connectome has many important topological features, such as small-world property, modularity, and hierarchy (Xia and He, 2017; Boccaletti et al., 2006; Ferrarini et al., 2009). We also identified that both groups showed efficient and economic small-world topology. However, no significant differences were found in small-world properties between two groups. Nevertheless, the CID patients showed smaller normalized C_p, E_{glob}, and E_{loc}, but larger normalized L_p compared with HCs. These altered small-world properties indicate a disturbance in network architecture of information transfer and processing across brain in CID patients. Therefore, our evidence of disrupted small-world properties might implicate declined memory and cognition
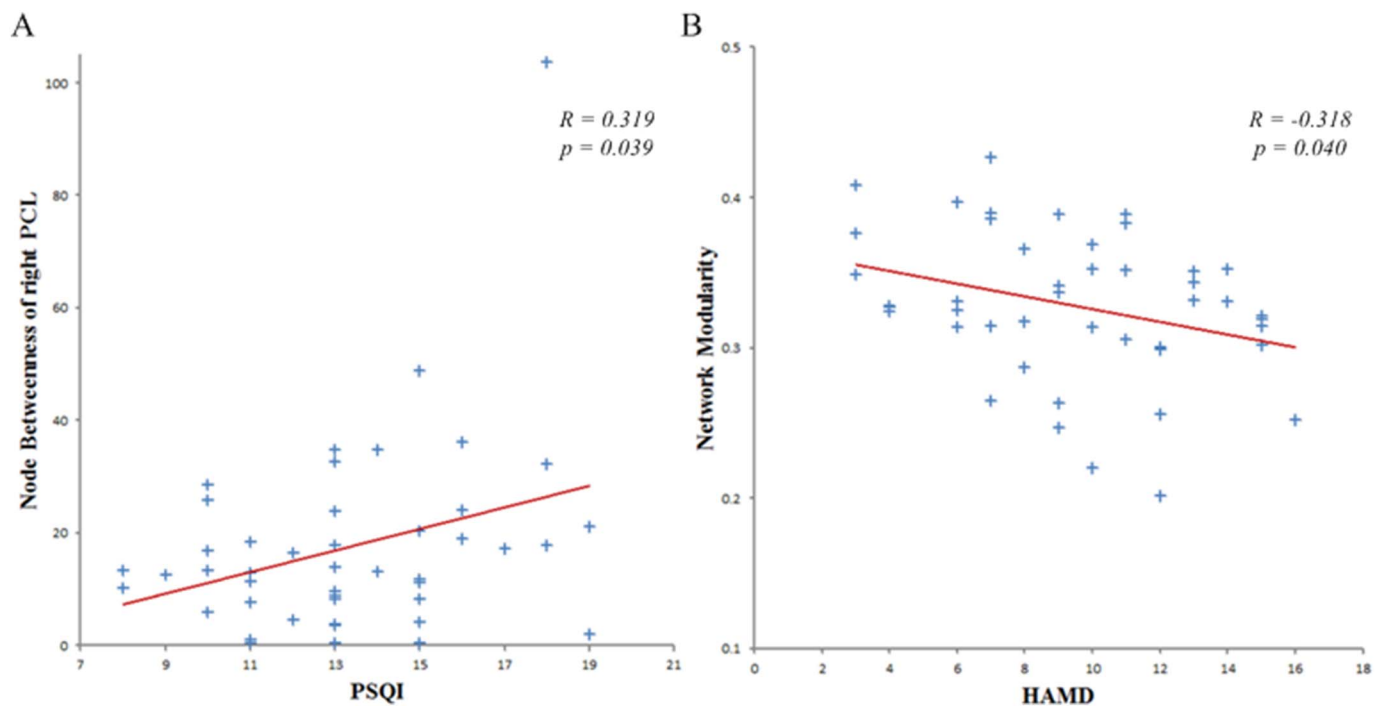
Fig. 3. (A) Scatterplot showing a significant positive correlation between CID patients PSQI scores and node betweenness of right PCL ($R = 0.319$, $P = .039$). (B) Scatterplot showing a significant negative correlation between CID patients HAMD scores and network modularity ($R = -0.318$, $P = .040$). Abbreviations: PSQI, Pittsburgh Sleep Quality Index; HAMA, Hamilton Anxiety Rating Scale; PCL, central paracentral Lobule; CID, chronic insomnia disorder.

performance in CID patients. From another point of view, these results guide us to understand the pathophysiological mechanisms of CID from the whole brain. No significant group difference was observed in terms of small-world property, which might be related to the severity of CID. CID is often accompanied with depression and anxiety (Taylor et al., 2005; Benca and Peterson, 2008). To eliminate the effects of them, we recruited CID patients that meet HAMA ≤14 scores and HAMD ≤17 scores in the present study. Furthermore, alterations in the small-world property caused by CID might be subtle.

Moreover, a decreased number of module and hierarchy was observed in CID patients. These properties have several advantages, including greater robustness, adaptivity, and evolvability of network function (Meunier et al., 2010). The highly modularized structures in CID patients and HCs in the current study provided further evidence for these advantages. Modular organization is defined as a subset of highly inter-connected nodes relatively sparsely connected to nodes in other modules (Boccaletti et al., 2006; Meunier et al., 2010). A decreased number of module and hierarchy in CID patients indicated relatively less inter-modular and intra-modular edges, including long and short distance connections. The disrupted topological modules may result in functional disruptions of CID patients, such as sleep, cognition, emotion, and memory. Additionally, network modularity was negatively correlated with HAMD score. Previous studies have demonstrated that insomnia and depression are intimately related (Taylor et al., 2005; Benca and Peterson, 2008). Therefore, the results may suggest an overlapping neurobiology between CID and depression disorder. Assortativity is defined by correlating the degree of each node to the mean degree of their neighbors (Newman, 2002; Braun et al., 2012). This topology property shows the relationship of degree between neighbor nodes within the network. Increased assortativity in the CID patients indicated increased interaction between different nodes. This result may be in line with "hyperarousal" model account of CID.

In addition to the global topologies, the node centralities of the brain functional connectome were also examined. Decreased nodal centralities were mainly located in the default mode network (DMN),

including left MFGorb, right MFGob and left angular, and dorsal attention network (DAN), including left opercular IFG and triangular IFG (Pang et al., 2017; Calster et al., 2016; Chou et al., 2016). The altered nodal characteristics indicated abnormalities of the roles of nodes in information transport and integration (Sporns et al., 2007). Thus, the abnormal nodal characteristic of different regions may cause dysfunction of network to which they belong. The DMN not only plays a central role in the modulation of consciousness but is also associated with cognitive domains, which are known to be affected by prolonged wakefulness, including memory, attention, and emotion processing (Suh et al., 2016). Prior studies indicated DMN disconnection in insomnia, including bilateral MFGorb and left angular (Pang et al., 2017). Other studies also found that CID patients showed lower ALFF and relative glucose metabolism in frontal-orbital gyrus compared with HCs (Dai et al., 2016; Kay et al., 2016). A number of neuroimaging studies have confirmed the close correlation between FC and cognitive impairment (Pang et al., 2017). Thus, the disrupted consciousness and cognitive function of DMN may be related to the changed node centralities in DMN. DAN is involved in top–down and goal-directed attentional control and closely related to many advanced cognitive tasks (Corbetta and Shulman, 2002). Opercular and triangular IFG have been reported to be involved in slow-wave sleep, which may mediate some of the functional benefits of sleep (Gemignani et al., 2012). Decreased FC and thickness of opercular IFG were found in CID patients compared with HCs (Geest et al., 2017; Zhao et al., 2015). Furthermore, decreased global and local FCs of triangular IFG were found in CID patients (Pang et al., 2017; Santarnecchi et al., 2013). These results indicated that the DAN functions had been disrupted from different aspects, including structure, global function, and local function, which may influence sleep quality and lead to decrease in cognitive function.

Increased nodal centralities were also found in some regions in the right hemisphere, including cuneus, PCL, hippocampus, ITG, and MCG. Cuneus is part of visual network (VN), which is involved in memory-related mental imagery and/or visual memory consolidation (Marques et al., 2017). Previous functional neuroimaging studies found increased

FC, ALFF, and ReHo in the right cuneus and indicated that CID involves dysregulated brain functioning robustly in cuneus (Kay and Buysse, 2017; Huang et al., 2012; Santarnecchi et al., 2013). PCL is mainly located in the sensory-motor network (SMN) (Jung et al., 2017). Individuals with insomnia fell into a perpetual cycle of somatic hyperarousal, and increased sensitivity to sensory stimulation, which leads to further cortical arousal and difficulty in sleep initiation and maintenance (Killgore et al., 2013). According to the hyperarousal theory of insomnia, difficulty in initiating or maintaining sleep was associated with greater FC within SMN (Killgore et al., 2013). Compared with HCs, CID patients showed not only increased nodal centralities of the right PCL but also significant positive correlation between node betweenness of right PCL and PSQI score. Even though the outliers influenced the significance of the results, the node betweenness of right PCL also showed significant correlations with some clinical data. Furthermore, insomnia has close relationship with depression, and anxiety (Taylor et al., 2005; Benca and Peterson, 2008; Alvaro et al., 2013). In summary, these results indicated that insomnia severity is associated with functional disruption of PCL, which may be a target for therapeutic intervention in pediatric CID. However, more studies are needed to confirm it.

Hippocampus belongs to DMN and is related to cognition performance, emotion processing, and memory formation, which play an important role in sleep regulation (De Havas et al., 2012; Noh et al., 2012; Walker and van Der, 2009). Several studies using rsfMRI found that the hippocampus is extensively connected with amygdala and superior frontal gyrus (Huang et al., 2012; Li et al., 2017; Pang et al., 2017). The impaired hippocampus may have increased interaction with other regions to meet the need of cognition performance, emotion processing, and memory formation. The ITG is the last cortical area along the ventral visual pathway involving visual perception and a part of DMN (Calster et al., 2016; Onitsuka et al., 2004). The increased ReHo has been reported to be useful for indexing the extent of insomnia traits and mood state (Dai et al., 2014). The increased nodal centralities of ITG in the present study confirmed previous results and may be related to the hyperarousal reactivity of CID. Increased or decreased nodal centralities of DMN regions were found in our study, and these conditions may be related to unbalanced resting-state networks activity in the DMN of CID, which was demonstrated by previous studies (Kay and Buysse, 2017; Marques et al., 2017). MCG is an important region of the limbic system and related to emotion processing (Wang et al., 2016c). The disrupted emotion regulation function of CID may be related to altered nodal centralities of right MCG.

Five connections within the ten brain regions of altered node centralities which composed a CID-related sub-network were significantly changed. The decreased connections were mainly located within DMN, while increased connections were mainly located between DMN and SMN or limbic system. The DMN plays a central role in the modulation of consciousness, and is associated with the self-referential mental activity, emotional and episodic memory processing, or mind wandering when individuals are not focusing on the external environment (Nie et al., 2015). Taking previous evidences of impaired DMN into consideration, we speculated that the cognitive, emotion, and memory impairment of CID may be associated with the decreased connections within DMN. Prior study indicated that sleep-deprived subjects can mobilize the IFG more effectively during encoding to meet the need of more efficient memory formation (Yoo et al., 2007). The increased connections between DMN and SMN or limbic system may represent a compensatory mechanism to overcome the negative effects of sleep deficits and maintain the psychomotor and cognition performances. Two previous studies showed the abnormal FCs across the brain in CID patients (Li et al., 2017; Pang et al., 2017). Those results are almost consistent with the current study but not exactly the same. The differences could perhaps be due to the diverse methodological approaches, patient sampling, or data quality.

5. Limitations and strengths

Several limitations underlie the above results. First, due to adopting binary network model without weight, much valuable information could be missed. Therefore, future research should pay more attention to explore a more realistic weighted network model. Second, alterations in the FC network did not survive the stringent FDR correction, which may result from our relatively small sample. Thus, future studies with larger sample size are needed. Third, we only used the AAL atlas including 90 regions to analyze the topological organization of brain functional connectomes. However, network properties are sensitive to nodal definition based on parcellation strategies and spatial scales (Wang et al., 2011). More robust parcellation scale and test–retest reliability atlas should be explicitly investigated into in the future work. Fourth, we recruited CID patients and HCs by a specialized neurologist and some subjective scale (PSQI, HAMA, and HAMD). However, the objective sleep measure of polysomnographic (PSG) was not employed in our studies. Thus, future studies need to adopt strictly objective assessments (such as PSG) to recruit CID patients. Fifth, even though the participants were given detailed instructions and training before the experiment and asked about their states during scan after the experiment, we could not ensure sleep–wake state of subjects during the resting state scan without fMRI compatible EEG. Future studies need to take some measures to monitor subjects state. Last, there are two outliers in the node betweenness of right PCL, which influenced the significance of the correlation results to some extent.

6. Conclusions

The present study is based on the graph theory to testify disrupted topological organization in the brain functional connectome in CID. The results indicated a decreased number of module and hierarchy and increased assortativity. Moreover, CID patients showed altered nodal centralities in many brain regions mainly implicated in behavioral, emotional, and cognitive function, and these regions are located in DMN, DAN, and SMN. The results suggest that functional disruptions of CID patients may be correlated to the disruptions in global and regional topological organization of the brain functional connectome, and shed new light to the pathophysiological mechanisms of CID.

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Disclosure statement

QTY and TB are employees of Siemens Healthcare. The other authors declare no conflict of interests regarding the publication of this paper. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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