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Original Article

ORIGINAL ARTICLE

Resting-state brain network topological properties and the correlation with neuropsychological assessment in adolescent narcolepsy

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Abstract

Study Objectives: To evaluate functional connectivity and topological properties of brain networks, and to investigate the association between brain topological properties and neuropsychiatric behaviors in adolescent narcolepsy.

Methods: Resting-state functional magnetic resonance imaging (fMRI) and neuropsychological assessment were applied in 26 adolescent narcolepsy patients and 30 healthy controls. fMRI data were analyzed in three ways: group independent component analysis and a graph theoretical method were applied to evaluate topological properties within the whole brain. Lastly, network-based statistics was utilized for group comparisons in region-to-region connectivity. The relationship between topological properties and neuropsychiatric behaviors was analyzed with correlation analyses.

Results: In addition to sleepiness, depressive symptoms and impulsivity were detected in adolescent narcolepsy. In adolescent narcolepsy, functional connectivity was decreased between regions of the limbic system and the default mode network (DMN), and increased in the visual network. Adolescent narcolepsy patients exhibited disrupted small-world network properties. Regional alterations in the caudate nucleus (CAU) and posterior cingulate gyrus were associated with subjective sleepiness and regional alterations in the CAU and inferior occipital gyrus were associated with impulsiveness. Remodeling within the salience network and the DMN was associated with sleepiness, depressive feelings, and impulsive behaviors in narcolepsy.

Conclusions: Alterations in brain connectivity and regional topological properties in narcoleptic adolescents were associated with their sleepiness, depressive feelings, and impulsive behaviors.

Statement of Significance

The neural mechanisms behind psychopathological behaviors in narcolepsy have become a topic of increasing interest. This report extends on findings regarding the connectivity and topological properties of resting-state brain networks in adolescent narcolepsy specifically. Depression and impulsivity were measured by questionnaires in adolescent narcolepsy. Our findings, therefore, provide important relationships between resting-state brain networks and the neurobehavioral characteristics in adolescent narcolepsy.

Key words: narcolepsy; independent component analysis; graph theory analysis; network-based statistics; sleepiness; depression; impulsivity

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Introduction

Narcolepsy is a chronic neurological disease, which is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucination. Deficiency in endogenous hypocretin due to degeneration in the hypothalamus is thought to be the core pathophysiology of narcolepsy. Previous functional brain imaging studies in narcolepsy patients have found altered brain structures [1–8], blood oxygen level dependent (BOLD) signaling [9–12], and brain metabolism [13–15].

In drug-naïve narcolepsy patients, a widespread disrupted white matter integrity of frontal lobes related to depressive symptomatology [2]. Recently, white matter deficiencies, such as in the inferior fronto-occipital fasciculus tract, the anterior-medial temporal lobes, and the midbrain regions, were reported [7, 8]. These are known to be involved in key cognitive and affective functions. Moreover, narcolepsy patients showed widespread abnormal white matter beyond the acknowledged focal hypothalamic deficiencies [5, 6]. As for the grey matter, reduced volume in the hippocampus and amygdala as well as cortical thinning in the prefrontal cortex, inferior parietal lobule and insula were reported [1, 3]. Furthermore, the hippocampal and amygdala atrophy was related to prolonged daytime sleepiness and decreased rapid eye movement (REM) sleep latency [1]. Recently, an absolute loss of the total anterior hippocampus volume in narcolepsy with cataplexy patients was found [4]. In addition, a longer duration of the disease significantly decreased the anterior hippocampus volume [4]. A large body neuropsychological evidence shows the involvement of the hippocampus in episodic memory and spatial functions. While the cortical thickness of the left supramarginal gyrus was associated with sleepiness, as assessed by the Epworth Sleepiness Scale (ESS) [3].

Other functional magnetic resonance imaging (fMRI) studies in narcolepsy patients demonstrated especially abnormal processing in the brain's emotional network. In two studies [10, 11], they showed increased BOLD responses to humorous stimuli in the amygdala, nucleus accumbens, and the insula. Ponz et al. observed that narcolepsy patients had abnormal activation in the reward system, that is, neural responses to expectancy and experience of monetary gains and losses [9]. While assessment of food-driven attention showed deficiencies in executive control being associated with the dorsal medial prefrontal cortex and ventral medial prefrontal cortex responses. The authors speculate that the overeating in narcolepsy patients could be attributed to abnormal food-related motivational brain responses [12].

Reduced cerebral perfusion and metabolism were found in subcortical structures, such as the hypothalamus and thalamus [13, 15]. Huang et al. demonstrated in young narcoleptic patients that hypo-metabolism in the mid-frontal lobe and angular gyrus is associated with sleepiness and neurocognitive performance [14]. These previous studies demonstrate brain alterations in narcolepsy being associated with sleepiness, mood, and neurocognition in both adults and youth.

Little is known about resting-state functional brain imaging in adolescent narcolepsy. Our previous study showed decreased fractional low-frequency fluctuations values in medial superior frontal gyrus, inferior parietal lobule, and supramarginal gyrus in both adult and juvenile narcolepsy patients compared with controls [16]. We also found in adult narcolepsy patients decreased functional connectivity within the executive and salience networks [17]. Several neuropsychiatric behaviors have been observed in narcolepsy, and the neural mechanism behind them has become a topic of growing interest [18]. Studies have shown that the role of hypocretin is not restricted to arousal reinforcing or feeding behavior [19–21], but also modulates stress reactions through stimulation of the hypothalamus–pituitary–adrenal axis [22] and motivated behavior [23]. For adolescent narcolepsy with reported psychiatric symptoms, research on their brain activity may reveal novel insights about the changing phenotype across this age range. The goal of this present study was first to find in adolescents characteristic changes in resting-state brain functional connectivity using independent component analysis (ICA) and graph theory analysis methods [24]. Second, we would relate these brain alterations to their neuropsychiatric behaviors. We hypothesize that alterations in resting-state brain functional connectivity strongly associates with their neurobehavioral profile.

Materials and Methods

Participants

A total of 26 drug-naïve adolescent narcolepsy patients with cataplexy were recruited according to the International Classification of Sleep Disorders-3 [25] from the Sleep Medicine Center in Peking University People's Hospital. Another 30 healthy controls (group-matched on age and gender) [13, 15] were recruited from community by advertisement. This study was approved by the Ethical Committee of the Peking University People's Hospital.

Questionnaires

Epworth Sleepiness Score

The modified version of the ESS was used to measure daytime sleepiness in both narcolepsy patients and healthy adolescents [26]. ESS is a measure of a person's general level of daytime sleepiness (scores range from 0 to 24), with an ESS score >8 suggesting excessive sleepiness in adolescents [27]. The ESS was modified slightly in this study to be more applicable in adolescents: the description regarding "taking alcohol after lunch" was deleted in item No. 7 and the subject was considered to be "a passenger in the car" instead of "a driver" in item No. 8.

Center for Epidemiologic Studies Depression Scale for Children

Under the supervision of trained individuals with a degree in psychology, both narcolepsy subjects and healthy controls completed the Center for Epidemiologic Studies Depression Scale for Children (CES-DC) [28]. CES-DC is a 20-item self-report measure for the assessment of emotional, cognitive, and behavior-related symptoms of depression. All items are evaluated with 4-point response options (0 = "not at all," 1 = "a little," 2 = "some," 3 = "a lot"). Total possible scores range from 0 to 60, with higher CES-DC scores indicating increasing levels of depressive symptoms. The Chinese version of CES-DC has been found to have good reliability and construct validity among various Chinese populations [29].

Barratt Impulsivity Scale

The Barratt Impulsivity Scale (BIS) [30] was used to assess impulsiveness. The BIS consists of 30 items, scored on a 5-point scale. Total scores range between 30 and 150, with higher values

indicative of higher levels of impulsivity. In addition to yielding a total score, the structure of the BIS allows for the assessment of three subscales: "attentional impulsivity" indicating a lack of attention and an inability to tolerate cognitive complexity; "motor impulsivity" indicating the behavior of engaging in a spur of the moment and lack of perseverance in activities; and "non-planning impulsivity" indicating a lack of self-control and an inability to consider future consequences. The Chinese version of BIS has been demonstrated good test–retest reliability for both the total score and for the three subscale scores [31].

Imaging data acquisition

fMRI data were obtained on a 3T scanner (Siemens, Skyra, Germany) using an 8-channel brain phased-array coil. Resting BOLD magnetic resonance imaging (MRI) scans were obtained with gradient-echo planar imaging (repetition time = 2,030ms, echo time = 30ms, slice =33, flip angle = 90°, field of view = 224mm*224mm, matrix = 64*64, voxel size = 3.5*3.5*3.5), followed by a high-resolution T1-weighted structural imaging with the following parameters: repetition time = 1,900ms, echo time =2.55ms, flip angle =9°, field of view = 240 mm*240 mm, thickness = 1mm, voxel size = 1*1*1. All participants were asked to resist sleeping to remain fully awake [32, 33], not to move and keep eyes open, supervised by both a physician and a technician via video during the whole MRI scan.

Imaging data processing

Preprocessing of functional imaging data

Functional MRI data preprocessing was performed using the Data Processing & Analysis for Resting-State Brain Imaging V2.1 (DPABI V2.1 [34]), which works with Statistical Parametric Mapping (SPM8) implemented in the MATLAB R2013b (The Math Works, Inc., Natick, MA) platform. A total of 240 functional volumes were acquired in the resting BOLD fMRI scans for each subject. The first five functional volumes were discarded, then the remaining fMRI data were corrected for slice timing and realigned for head motion correction. Anatomical and functional images were first manually reoriented to the anterior commissure, and structural images were co-registered to the functional images for each subject using a linear transformation. Then the co-registered functional images were normalized to the standard Montreal Neurological Institute space template with a resampling voxel size of 3 mm × 3 mm × 3 mm. The normalized functional images were smoothed using a Gaussian filter 4 mm full width at half maxima. All smoothed images were filtered using typical temporal bandpass (0.01–0.1 Hz) to reduce low-frequency drift, physiological high-frequency respiratory and cardiac noise. Linear trends were removed within each time series of every voxel. Then the covariates were regressed out from the time series of every voxel, including the white matter signal, cerebrospinal fluid signal, 24 head motion parameters [35], and the global signal.

Independent component analysis

The human brain is composed of a vast network of neurons, which generate both high and low frequency fluctuations. ICA facilitates the effective extraction of distinct resting-state fMRI networks by employing mathematical algorithms to decompose the signal from whole brain voxels to spatially and temporally independent components [24]. To overcome the drawbacks of single subject ICA, group ICA using the dual regression approach was initiated [36]. In this study, group ICA was performed by Group ICA of fMRI Toolbox (GIFT) [37]. The numbers of components were automatically estimated by minimum description length criteria for all subjects, modified to consider the account spatial correlation [38]. Each component was different from the others due to the algorithm in ICA. Visual examination and spatial correlation values (correlation value > 0.4) between each component and the resting-state fMRI network templates from GIFT [37] were applied to determine which components belong to which kinds of resting-state fMRI network.

Graph theory analysis

Graph theory analysis is applied to establish mathematical models of complex network functions within human brain [36]. These networks have connections between various regions in the brain and its combined dynamics constitute a larger single network. Graph theory measures the topological properties of a special brain region or the whole brain network related to a particular function. In the graph theory analysis of this study, the whole brain was divided into 90 regions according to Automated Anatomical Labeling [39], and the mean time series for every region were extracted. Pearson's correlation coefficients for each pair of regions were calculated using the mean time series among each region, and Fisher's Z transformation was performed to turn the data into a normal distribution matrix. Then, a positive binary undirected connection functional brain network was constructed across a range of selected threshold value (called sparsity). Sparsity is defined as the existing number of edges in a graph divided by the maximum possible number of edges. The sparsity of the functional brain network was set ranging from 0.05 to 0.5 (with 0.05 as a step size) [40]. We calculated the following graph theory metrics in the binary brain network as followings: (1) small-world network parameters: the normalized clustering coefficient, the normalized characteristic path length, and small-worldness; (2) nodal topological properties: degree centrality (DC) and nodal efficiency (NE).

The resting-state brain network has been reported to be one of the small-world networks which lie somewhere between a random and a regular network, with high efficiency in both global and local scales [41]. The clustering coefficient of a network is a metric characterizing the segregation of network, and the path length of a network is the measurement of network information integration. The small-worldness is the ratio between normalized clustering coefficient and normalized characteristic path length, which is special for the small-world network. Nodal DC is defined as the number of edges linked to the node, and NE is defined as average efficiency between the index node and all other nodes in the network.

Statistical analysis

Descriptive analysis

Non-paired two-sample *t*-test or chi-square tests were used to detect group differences between narcolepsy and healthy controls in age, gender, body mass index (BMI), and questionnaire scores using SPSS 23 (Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$.

ICA: For group comparisons between narcolepsy and controls, a non-paired two-sample *t*-test was utilized to detect the group differences in connectivity within each component (resting-state fMRI network). A false discovery rate (FDR, $p < 0.01$) correction, for multiple comparisons using MATLAB, was applied.

Graph theory analysis: For group comparisons between narcolepsy and controls in small-world network parameters and nodal topological properties, a non-paired two-sample *t*-test was utilized with Bonferroni correction of $p < 0.05$ using MATLAB.

Principal component analysis (PCA): PCA was applied to reduce the dimensionality of a set of nodal topographical properties. We will focus on regions replicating significant group differences across both DC and NE. Values of DC and NE in these regions will be served as factors and factors with eigenvalue exceeding 1 will be retained, then a varimax rotation will be carried out to ensure that each component has minimal associations with the other components.

Network-based statistics: For group comparisons between narcolepsy and controls in region-to-region connectivity of the normal distribution matrix from graph theory analysis, we utilized network-based statistics (NBS), which deals with multiple comparisons by detecting clusters of connections that significantly differ across groups instead of testing individual connections. A family-wise error corrected *p*-value ($p < 0.05$) was computed for the size of the graph component using 5,000 permutation tests in network-based statistics.

Brain-behavior correlation analysis: We will correlate the behavioral variables such as ESS, CES-DC scores, BIS scores with (1) the nodal topological properties from PCA results and (2) the region-to-region connectivity from NBS results, using Pearson correlations. The level of significance was set at $p < 0.05$.

Results

Descriptive analyses

As shown in Table 1, there were significant group differences regarding BMI and all questionnaire scores. Narcolepsy adolescents reported more sleepiness, depressive mood and impulsiveness.

ICA

Each component was independently selected according to the templates presented by GIFT. A total 50 components were obtained, 10 of which were resting-state fMRI network: 2 components are from the default mode network (DMN), 3 components are from the visual network, 3 components are from the sensorimotor network, 1 component is from the auditory network, and 1 component is from the attention network (Figure S1). Decreased functional connectivity between left subcallosal gyrus and one component of DMN, and increased functional connectivity in bilateral calcarine fissure within one component of the visual network could be found in narcolepsy compared with healthy controls (Figure S2, Table S1, FDR correction, $p < 0.01$). There were no significant group differences in the other components.

Graph theory analysis

Compared with healthy controls, the clustering coefficient and small-worldness in narcolepsy were significantly decreased (Bonferroni correction, $p < 0.05$). Total 10 brain regions showed significant group differences across both DC and NE in nodal topographical properties, including increased nodal topological properties in bilateral anterior cingulate gyrus (ACG), bilateral caudate nucleus (CAU), right insula and decreased nodal properties in bilateral posterior cingulate gyrus (PCG), bilateral precuneus lobe (PCUN), and right inferior occipital gyrus (IOG) in narcolepsy (Table 2, Bonferroni correction, $p < 0.05$). The values of DC and NE in the 10 regions were derived and prepared for PCA.

PCA

Our primary approach to conduct PCA was to determine the number of components, which encompass DC and NE in the 10 regions. A total of five components were extracted (Table S2) and accounted for 87.7% of the total variance. Component one was composed of DC and NE in bilateral PCG. Component two included DC and NE in bilateral CAU. Component three represented DC and NE in bilateral ACG and right insular lobe. DC and

Table 1. Demography for narcolepsy patients and healthy controls

	Narcolepsy	Healthy controls	P-value
Gender(female/male)	5/21	6/24	0.942
Age (years)	13.9 ± 2.7	13.3 ± 2.3	0.324
BMI	25.7 ± 4.8	18.9 ± 3.7	<0.001*
ESS	15 ± 3.4	5.5 ± 1.3	<0.001*
CES-DC score	18.1 ± 8.5	10.9 ± 5.7	0.025*
Motor BIS score	37.8 ± 17.1	23.4 ± 8.8	0.001*
Attentional BIS score	48.6 ± 14.9	29.8 ± 10	0.022*
Non-planned BIS score	58.6 ± 18	35.6 ± 9.7	<0.001*
Total BIS score	48.7 ± 13.9	29.6 ± 7.4	0.001*

A total of 25 narcolepsy subjects completed BIS-11 questionnaire and 22 narcolepsy subjects completed CES-DC questionnaire. All the healthy controls completed the total neuropsychological assessments.
BMI, Body Mass Index. ESS, Epworth Sleepiness Scale. CES-DC, Center for Epidemiologic Studies Depression Scale for Children. BIS, Barratt Impulsivity Scale.

Table 2. Brain regions showed significant group differences across both DC and NE between healthy controls and narcolepsy

	Brain region
Narcolepsy > controls	Left ACG
	Right ACG
	Left CAU
	Right CAU
	Right insula
Controls > narcolepsy	Left PCG
	Right PCG
	Left PCUN
	Right PCUN
	Right IOG

NE in bilateral PCUN were extracted separately as component four. DC and NE in right IOG were extracted separately as component five.

NBS

NBS identified a network cluster of significantly increased or decreased region-to-region connectivity in narcolepsy compared with controls (Figure 1, A). The network cluster of decreased connectivity in narcolepsy patients consisted of superior frontal gyrus, putamen, insula, hippocampus, superior and middle temporal gyrus, primary sensory cortex (postcentral gyrus), supplementary motor cortex, parietal lobe (supra-marginal gyrus, angular gyrus, and PCUN), and occipital lobe (calcarine fissure, lingual gyrus, and IOG, Figure 1, C). NBS additionally identified a cluster of increased connectivity in narcolepsy patients consisting of middle and inferior frontal gyrus, CAU, primary motor cortex (precentral gyrus), supplementary motor cortex, hippocampus and parahippocampal gyrus, superior and middle temporal gyrus, parietal lobe (supra-marginal gyrus, angular gyrus and PCUN), and IOG (Figure 1, B).

Brain-behavior correlation analysis

ESS negatively correlated with nodal topological properties in bilateral PCG (component one from PCA results, $r = -0.31$, $p = 0.021$, Figure 2, A). ESS positively correlated with nodal topological properties in bilateral CAU (component two from PCA results, $r = 0.33$, $p = 0.013$, Figure 2, B). Attentional BIS score positively correlated with nodal topological properties in bilateral CAU ($r = 0.29$, $p = 0.032$, Figure 2, C). Attentional BIS score negatively correlated with nodal topological properties in right IOG (component five from PCA results, $r = -0.3$, $p = 0.027$, Figure 2, D). These correlations remained significant after controlling for the effect of age, gender, and BMI.

Average decreased/increased connectivity values weights in the network cluster identified with NBS associated with ESS, CES-DC score, and total BIS score, respectively (Figure 3). These

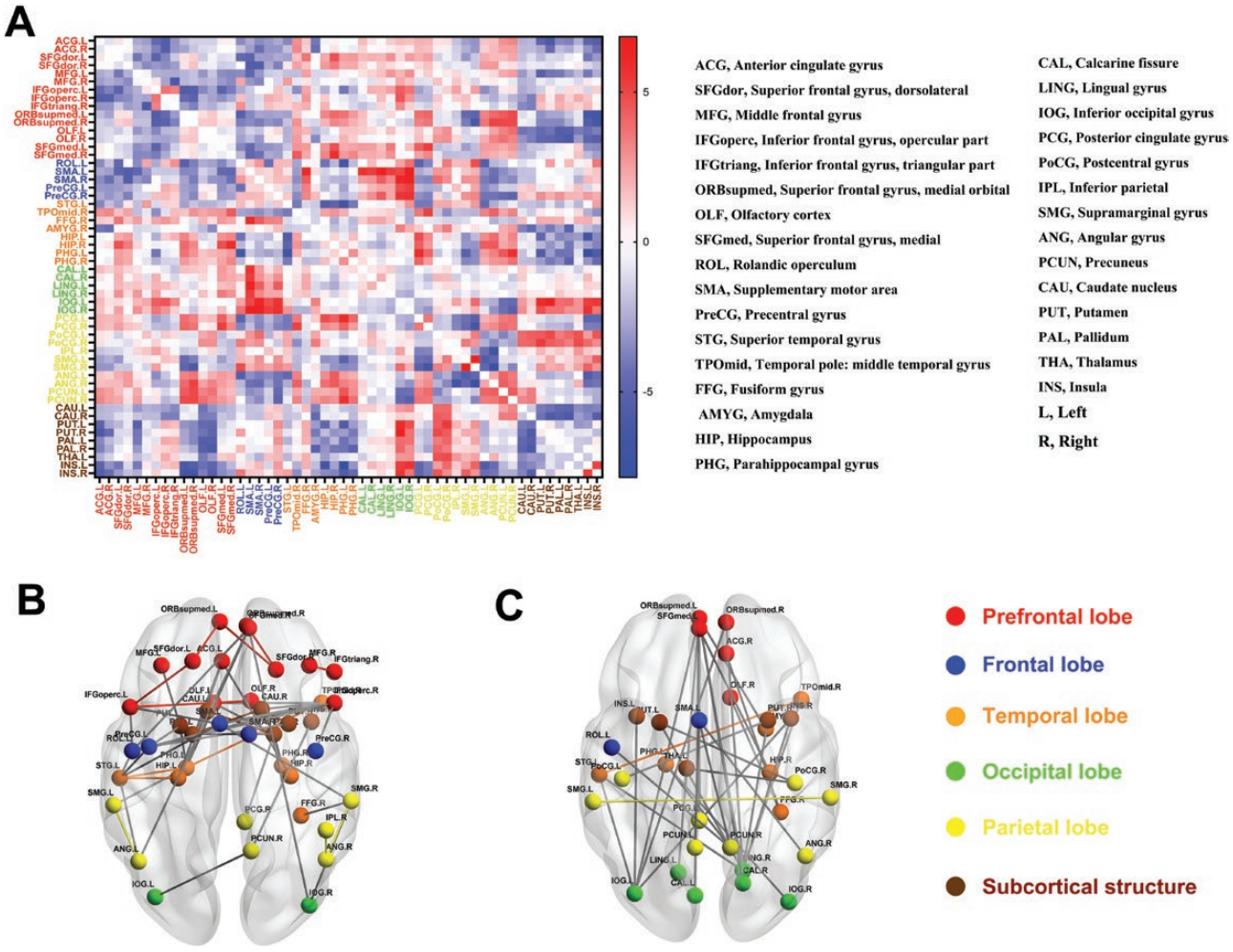

Figure 1. Network-based statistics results about group differences in region-to-region connectivity. (A) T value matrix of group differences in region-to-region connectivity after network-based statistics (family-wise error correction after 5,000 permutation tests, $p < 0.05$). Different font colors mean different brain areas: red means the prefrontal lobe; blue means frontal lobe; orange means temporal lobe; green means occipital lobe; yellow means parietal lobe; and brown means subcortical structure (basal ganglia and insula). As for the T value matrix, the absolute T value greater than 4.86 is considered significantly after network-based statistics. The positive T value (red in the matrix) means decreased connectivity in narcolepsy compared with controls, and the negative T value (blue in the matrix) means increased connectivity in narcolepsy compared with controls. The cluster of increased functional connectivity in narcolepsy compared with healthy controls was shown in (B) and a cluster of decreased functional connectivity in narcolepsy compared with healthy controls was shown in (C).

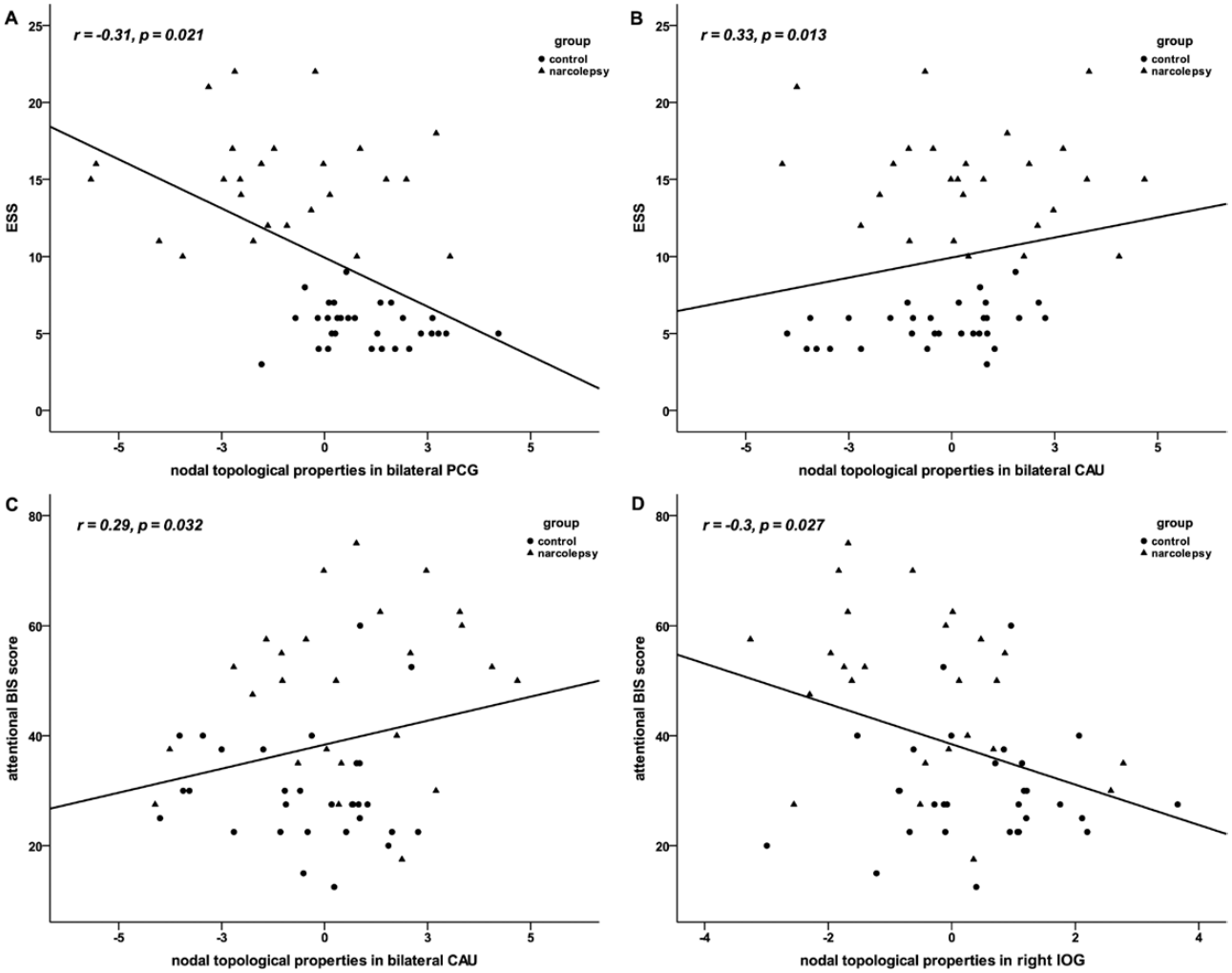

Figure 2. Correlation analysis between questionnaires scores and nodal brain network properties from PCA results. ESS, Epworth Sleepiness Scale. CES-DC, Center for Epidemiologic Studies Depression Scale for Children. BIS, Barratt Impulsivity Scale. CAU, caudate nucleus. PCG, posterior cingulate gyrus. IOG, inferior occipital gyrus.

correlations remained significant after controlling for the effect of age, gender, and BMI.

Discussion

In the current study, using ICA, we found in narcolepsy patients decreased functional connectivity between the left subcallosal gyrus and DMN, and increased functional connectivity in the visual network. Using graph theory analysis, narcolepsy patients exhibited decreased normalized clustering coefficient and small-worldness in small-world network parameters. The nodal topological properties revealed group differences in bilateral ACG, PCG, PCUN, CAU, and right IOG, insula. Using NBS, we identified a network cluster of increased or decreased connectivity in narcolepsy compared with healthy controls.

Our adolescents with narcolepsy presented in addition to sleepiness, depressive symptoms, and impulsiveness. Adolescents with narcolepsy are at higher risk for psychosocial disorders, such as behavioral problems, emotional problems with depression, and social difficulties [42–44]. Firstly, psychological disorders have been associated with reduced nighttime REM sleep latency, increased REM sleep pressure, nocturnal sleep fragmentation, and hallucinations in narcolepsy [23]. Secondly, mood disturbances and psychologic alterations could be triggered by hypocretin deficiency [22, 45]. Prior studies indeed showed that lower hypocretin levels correlated with the severity of depressive symptoms and the prevalence of attempted suicide [22, 46]. Perhaps decreased hypocretin level reduces signaling in reward and motivation pathways potentially contributing to depression, as perturbed activation in the reward system was found [9]. Sleepiness may increase risk-taking behavior in narcolepsy with cataplexy, and there was furthermore a trend toward higher scores of impulsiveness in narcolepsy without cataplexy compared with healthy controls after sleep deprivation [47]. Therefore, it is proposed that hypocretin deficiency alone would not explain the impulsiveness found in narcolepsy and that the contribution from the degree of sleepiness should be considered.

Using ICA, our adolescents showed significantly decreased functional connectivity between left subcallosal gyrus and DMN. Previously, the subcallosal gyrus (or subcallosal cingulate cortex) has consistently emerged as a core and well-connected component of the limbic system, which modulates emotional behavior [48]. The limbic system is furthermore connected with different nodal points in regard to sleep organization and arousal

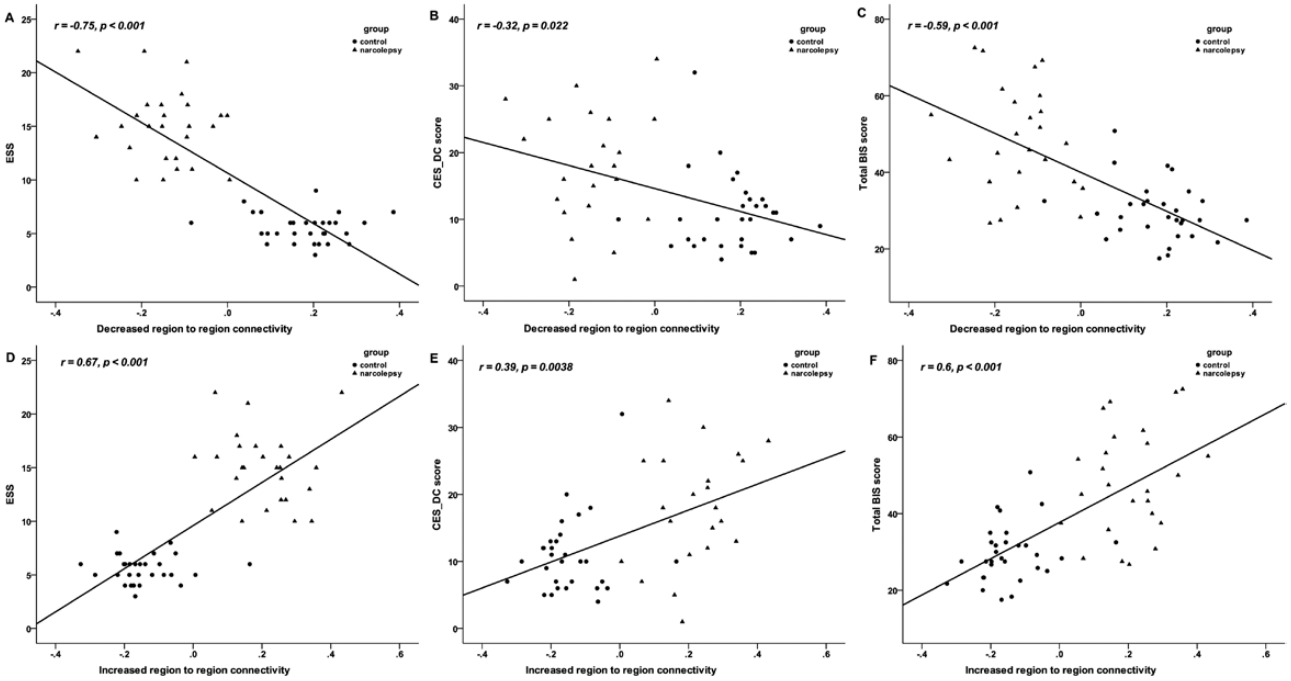

Figure 3. Correlation analysis between questionnaires scores and average increased/decreased region-to-region connectivity in narcolepsy. ESS, Epworth Sleepiness Scale. CES-DC, Center for Epidemiologic Studies Depression Scale for Children. BIS, Barratt Impulsivity Scale.

mechanisms [49]. Hence, the decreased connectivity between subcallosal gyrus and DMN found, may suggest impaired emotion and sleep-arousal regulation considering the limbic-DMN interaction. Alternatively, three previous neuroimaging studies in narcolepsy have reported hyper-metabolism in visual cortex [14, 32, 33], which were considered to be associated with the subjective effort to resist falling asleep during the scanning process. Our findings of increased functional connectivity in the visual network may, therefore, demonstrate the availability of this system to be recruited for staying awake.

We compared the small-world network parameters of narcolepsy subjects using data-driven graph-theoretical analysis. The adolescent narcolepsy subjects exhibited reduced clustering coefficient and small-worldness in small-world network parameters compared with healthy controls. More specifically, decreased small-worldness may reflect the imbalance of separation and integration in brain network function, indicating the impaired information processing in narcolepsy. Given that the clustering coefficient is a measure for functional differentiation in a network, it may represent the capacity for information distribution. The decreased clustering coefficient found in our sample may demonstrate the reduction in information segregation in the whole brain, with a corresponding impaired local information integration. The combination of decreased clustering coefficient and small-worldness indicates a disruption in the normal small-world network balance and suggests a tendency to the random network configuration of the brain network in narcolepsy. In our previous study, there was no significant difference in the small-world parameters between adult narcolepsy patients and healthy controls [17]. This may suggest a dramatic change in brain network information processing from adolescence to adulthood in narcolepsy.

The nodal topological properties analyses indicated a reduced number of connections and decreased communication efficiency in bilateral PCG, bilateral PCUN, and right IOG with other brain regions in narcolepsy. Whereas increased nodal topological properties can be found in bilateral ACG, bilateral CAU, and right insula in narcolepsy. Noteworthy, both the PCG and PCUN are the core nodes in DMN, which showed disruption in narcolepsy as discussed above. Also decreased nodal degree and efficiency in PCG have been detected in adult narcolepsy subjects [17]. Nodal topological properties in bilateral PCG are negatively associated with ESS of our adolescents, which suggests the involvement of bilateral PCG alterations in narcolepsy sleepiness. Regional topological properties in right IOG are negatively associated with attentional impulsiveness, which suggests the involvement of right IOG alterations in narcolepsy subjects' attentional impulsiveness.

Regions showing enhanced nodal degree and efficiency were closer to the salience network, a finding that is consistent with previous results [17, 32, 33]. The salience network involves the integration of sensory systems, affective and cognitive control, and tonic alertness maintenance [50–52]. The increased nodal topological properties identified in narcolepsy close to the salience network reinforced its major role in the conservation of arousal level, reflecting the patients' effort to keep alertness/awake. The positive correlations with ESS and attentional BIS scores demonstrate the involvement of bilateral CAU alterations in narcolepsy sleepiness and attentional impulsiveness.

Region-to-region connectivity and network-based statistics identified network clusters of increased and decreased connectivity in narcolepsy compared with healthy controls. More specifically, a cluster of increased connectivity mainly located within the salience network in the front brain regions (middle and inferior frontal gyrus, CAU, precentral gyrus, and supplementary motor cortex, Figure 1, B). The majority of decreased connectivity is between the front and back brain regions, parts of which are within the DMN (supra-marginal gyrus, angular

gyrus, and PCUN, Figure 1, C). Such region-to-region connectivity can be partially interpreted as alterations in the salience network and DMN in narcolepsy. When considering the role of the salience network and DMN in affective regulation and wakefulness maintenance [50, 52–54], the correlations found with ESS, CES-DC, and total BIS scores suggest their importance in the psychopathological profile of narcolepsy in youth. It indicates the relationship between neuropsychiatric behaviors and brain network organization in adolescent development [55].

Several limitations of this study should be listed. Although narcolepsy is a rare disease, the number of subjects remains relatively small for this study to fully capture "adolescence." To avoid the confounding risk of falling asleep, a simultaneous fMRI-EEG technique should have been performed. A dynamic functional connectivity analysis could be preferred detecting the change of connection in narcolepsy brain networks over time. Lastly, further research is warranted to clarify how hypocretin deficiency affects the connectivity in brain networks, as we did not collect biomarkers in this sample.

Conclusion

In conclusion, in youth with narcolepsy, sleepiness with depressive and impulsive behaviors were detected. Adolescent narcolepsy patients exhibited disrupted small-world network properties and disrupted limbic-DMN connectivity. Regional alterations in CAU and PCG were associated with subjective sleepiness and impulsiveness. Remodeling within the salience network and the DMN associated with sleepiness, depressive feelings, and impulsive behaviors in narcolepsy. Our findings highlight the role of brain functional connectivity and topological properties in the association with neuropsychiatric behaviors in narcolepsy.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement. The authors declare that they have no competing interests.

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