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Original Article

ORIGINAL ARTICLE

Altered cerebrocerebellar functional connectivity in patients with obstructive sleep apnea and its association with cognitive function

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Abstract

Study Objectives: Previous functional MRI studies have reported altered brain networks in patients with obstructive sleep apnea (OSA). However, the extent and pattern of abnormal connectivity were inconsistent across studies, and cerebrocerebellar connections have been rarely assessed. We investigated functional network changes in cerebral and cerebellar cortices of OSA patients.

Methods: Resting-state functional MRI, polysomnography, and neuropsychological (NP) test data were acquired from 74 OSA patients (age: 45.8 ± 10.7 years) and 33 healthy subjects (39.6 ± 9.3 years). Connectivity matrices were extracted by computing correlation coefficients from various regions of interest, and Fisher *r*-to-*z* transformations. In the functional connections that showed significant group differences, linear regression was conducted to examine the association between connectivity and clinical characteristics.

Results: Patients with OSA showed reduced functional connectivity (FC) in cerebrocerebellar connections linking different functional networks, and greater FC in cortical between-network connections in prefrontal regions involving the default mode network (DMN) and the control network. For OSA group, we found no correlation between FC and sleep parameters including lowest SaO_2 and arousal index in the connections where significant associations were observed in healthy subjects. FC changes in DMN areas were related to reduced verbal fluency in OSA. Lower local efficiency and lower clustering coefficient of the salience network in the left cerebellum were also observed in OSA.

Conclusions: OSA affects mainly the cerebrocerebellar pathway. The disruption of function in these connections are related to sleep fragmentation and hypoxia during sleep. These abnormal network functions, especially DMN, are suggested to participate in cognitive decline of OSA.

Statement of Significance

Several resting-state functional MRI studies in obstructive sleep apnea (OSA) have shown dysfunctional connectivity in various regions, but cerebrocerebellar connections have been rarely assessed. In this study, we investigated changes in whole brain functional connectivity (FC) of multiple functional networks of OSA patients using fine parcellation of brain functional areas including the cerebellum. It enabled us to identify the novel pattern of changes in cerebrocerebellar connections and impaired integration of cerebellar networks, as well as greater FC in prefrontal regions involving the default mode network for OSA patients. Interestingly, these altered connections were associated with sleep parameters and cognitive performance of OSA patients. Our results could provide new insight into the pathophysiology of OSA and the cognitive impairment following OSA.

Key words: obstructive sleep apnea; resting-state fMRI; brain networks; functional connectivity; cognitive function

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Introduction

Obstructive sleep apnea (OSA) is a common condition, characterized by recurrent episodes of partial or complete obstruction of the upper airway. Repetitive apneas and hypopneas cause intermittent hypoxemia and hypercapnia, as well as microarousals and sleep fragmentation [1, 2]. These factors are thought to further lead to oxidative stress, persistent systemic inflammation, oxygen sensor activation, and increase of sympathetic activity, eventually resulting in OSA-related brain structural and functional alterations, as well as impairments in various cognitive domains including memory, executive function, and attention [3, 4]. Yet, the exact pathophysiological mechanisms underlying neuropsychological comorbidities in OSA remain unclear [5].

Abundant neuroimaging studies have investigated the pathophysiology of OSA by exploring gray matter (GM) volume and concentrations [6, 7], the white matter (WM) integrity [8, 9], cerebral metabolism [10, 11], and regional cerebral blood flow [12]. In these studies, alterations in multiple brain structures that were associated with memory and executive functions (i.e. cingulum, prefrontal, parieto-occipital, temporal area, and hippocampus) were observed in OSA patients. Unlike structural MRI, where morphological changes of brain regions are assessed in relation to neuronal and cytoarchitectural damage, resting-state functional magnetic resonance imaging (rs-fMRI) offers approaches that allow us to identify large-scale brain network aberrations in a variety of neurological and neuropsychiatric disorders by looking at changes in blood-oxygen-level-dependent (BOLD) signal [13, 14]. Resting-state functional networks have implications for sleep and sleep disorders. This may be partly because the resting "state" has been seen as a dynamic mixture of wakefulness and different sleep stages [15, 16]. Furthermore, alterations in connectivity of the resting-state networks, such as the default mode network (DMN), have been identified after sleep disruptions [17, 18] and sleep deprivation [19, 20], as well as in those with OSA [21, 22]. Previous rs-fMRI studies in OSA have shown dysfunctional connectivity in various brain regions which may be linked to cognitive and emotional functions that are frequently impaired in patients with OSA [21, 23–29]. However, the extent of such abnormal connectivity and the pattern of bidirectional changes (increased or decreased functional connectivity [FC]) have been inconsistent among the studies.

Such inconsistencies might be attributed to differences in analysis methods and patient group characteristics including sample size, age range, body mass index (BMI), and gender distribution among studies. One notable limitation of the previous rs-fMRI studies of OSA is that the cerebellar network has been rarely explored despite cerebellar regional changes in OSA subjects that were revealed in a number of structural MRI studies [7, 8]. It is indeed well-accepted that the cerebellum participates in cognitive networks involving the prefrontal and parietal association cortices [30], which are frequently found to be structurally abnormal in OSA [7, 8], encouraging us to investigate cerebellar networks in OSA subjects.

In the current study, we aimed to systematically analyze brain networks using rs-fMRI and investigate changes in cerebral, cerebellar, and cerebrocerebellar functional networks of OSA patients. We assessed the OSA patients' FC and network parameters within and between multiple networks compared with healthy subjects. We then assessed whether such alterations correlated with clinical characteristics and neuropsychological deficits in OSA.

Methods

Participants

We recruited 99 newly diagnosed, treatment-naïve male OSA subjects (apnea–hypopnea index [AHI] ≥ 15) from the Sleep clinic of Samsung Medical Center and 36 male good sleepers (healthy subjects). Each subject had a detailed clinical interview, sleep questionnaire, and overnight polysomnography (PSG). A total of 21 patients were excluded according to the following criteria: (1) respiratory diseases, (2) history of malignancy, (3) history of coronary heart disease or cerebrovascular disease, (4) other neurological (neurodegenerative diseases, epilepsy, and head injury) or psychiatric diseases (psychosis and current depression), (5) alcohol or illicit drug abuse or current intake of psychoactive medications, and (6) a structural lesion on previous brain MRI (Figure 1). A total of 78 OSA and 36 healthy subjects underwent MR scans with a study protocol. Four OSA and three healthy subjects were excluded due to severe motion artifacts in the MR images. Finally, 74 OSA and 33 healthy subjects were included in our study. Even though OSA and healthy subjects were mostly middle-aged men, the healthy group was significantly younger than the OSA subjects (p = 0.004). Age was thus considered as a covariate in our statistical analyses (details explained later). Written informed consent was obtained from all participants, and the Institutional Review Board of Samsung Seoul Hospital authorized the study protocol and design (IRB NO. 2017-02-126).

Overnight PSG

PSG was recorded with Somnologica (Embla, Denver, CO) using a six-channel electroencephalogram, a four-channel electrooculogram, electromyogram, and electrocardiogram. A thermistor, a nasal air pressure monitoring sensor, an oximeter, piezoelectric bands, and a body position sensor were also applied to the participants. Apnea was defined as a reduction in airflow by 90% or more lasting at least 10 s. Hypopnea was defined as a reduction in airflow by 30% or more lasting at least 10 s and accompanied by at least 3% oxygen desaturation compared with baseline or respiratory arousal [31].

Neuropsychological assessments

OSA and healthy groups underwent a battery (2.5 h) of neuropsychological tests. The neuropsychological tests consisted of

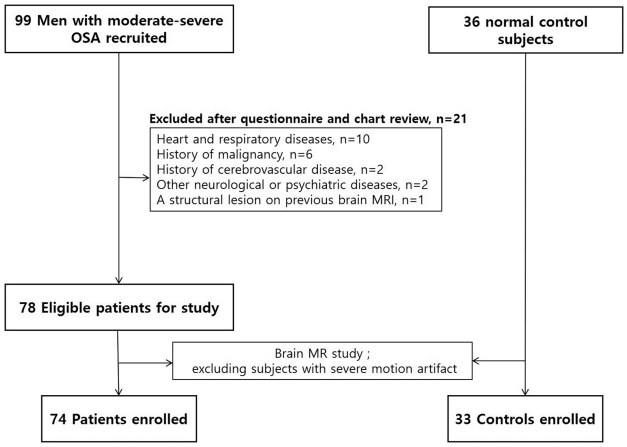

Figure 1. Flow chart to explain the patient enrollment and exclusion criteria.

digit span tests from the Wechsler Memory Scale-Revised [32], the Corsi block tapping tests (forward and backward) [33], the Trail Making Tests A and B [34], the Stroop test [35] for attention and executive function, the Controlled Oral Word Association Test for verbal fluency function [36], the Korean California Verbal Test [37, 38], and the Rey Complex Figure Test for verbal and visual memory function [39]. Composite scores were computed for each domain by transforming the neuropsychological test scores into standardized z-scores and averaging this data. To examine emotional state, the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) were administered on the day of the sleep study [40, 41].

Brain MRI acquisition

All subjects underwent 3T MRI using an identical scanner (Ingenia, Philips, the Netherlands). Patients were instructed to remain awake and relaxed with their eyes open and fixed to a given point. T1-weighted structural data and rs-fMRI data were acquired with an echo planar imaging (EPI)-BOLD sequence in the axial plane. The parameters for T1-weighted structural MRI acquisition were as follows: repetition time (TR) = 9.9 ms; echo time (TE) = 4.6 ms; field of view = 240 × 240 mm^2; flip angle = 8°; matrix size = 240 × 240; slice thickness = 0.5 mm; and voxel size = 1.0 × 1.0 × 0.5 mm^3. The parameters for rs-fMRI were as follows: TR = 3000 ms; TE = 30 ms; field of view = 220 × 220 mm^2; flip angle = 90°; matrix size = 76 × 76; slice thickness = 4 mm; pixel resolution = 1.72 × 1.72 × 4 mm^3. All MRI data were acquired at an intermediate time from 08:00 am to 02:00 pm.

fMRI data preprocessing

Preprocessing of rs-fMRI data was conducted using Analysis of Functional NeuroImages (AFNI; https://afni.nimh.nih.gov) software [42]. First, the initial five volumes from each rs-fMRI data were removed. Physiologic Estimation by Temporal ICA (PESTICA; https://www.nitrc.org/projects/pestica) was used to identify and correct for physiological cardiac and respiratory noise of the rs-fMRI [43, 44]. After removing physiological noise, data were de-spiked, and corrected for slice time acquisition differences and head motion [45]. Data with inter-TR motion over 1.5 mm or estimated maximum displacement of more than 3 mm were excluded. The remaining effects of noise signals, including head motion inference, non-GM signals (time series from ventricle mask), and hardware-related artifact (localized regressor from eroded WM mask) were also corrected using the anatomy-based correlation corrections (ANATICOR) method [46]. Subsequently, the cleaned data were processed using a band-pass filter ($0.01 < f < 0.1$). These data were then co-registered to the anatomical T1-weighted image using the cost function computed by the spatially weighted correlation method [47], and normalized into the ICBM-Montreal Neurological Institute (MNI) template space. The normalized data were spatially smoothed with a kernel size of 6 mm of full-width-at-half-maximum (FWHM).

Brain network construction

Nodes were defined with 234 regions corresponding to 17 functional networks parcellated using resting-state FC that has been previously defined [48]. The nodes included 200 cortical parcels defined by Schaefer et al. [49], as well as 34 parcels of the left and right cerebellum from Buckner et al. [50]. Figure 2 represents the 234 regions of interest (ROIs) used in this work. Finally, for each individual, we obtained a cross-correlation symmetry matrix (234 × 234) that reflected the FC between regions. The matrix was converted into a z-value using Fisher's *r*-to-*z* transformation.

Statistical analysis

To compare demographics, underlying diseases mood questionnaires, PSG parameters, and neuropsychological scores between OSA patients and healthy subjects, Student's *t*-test for

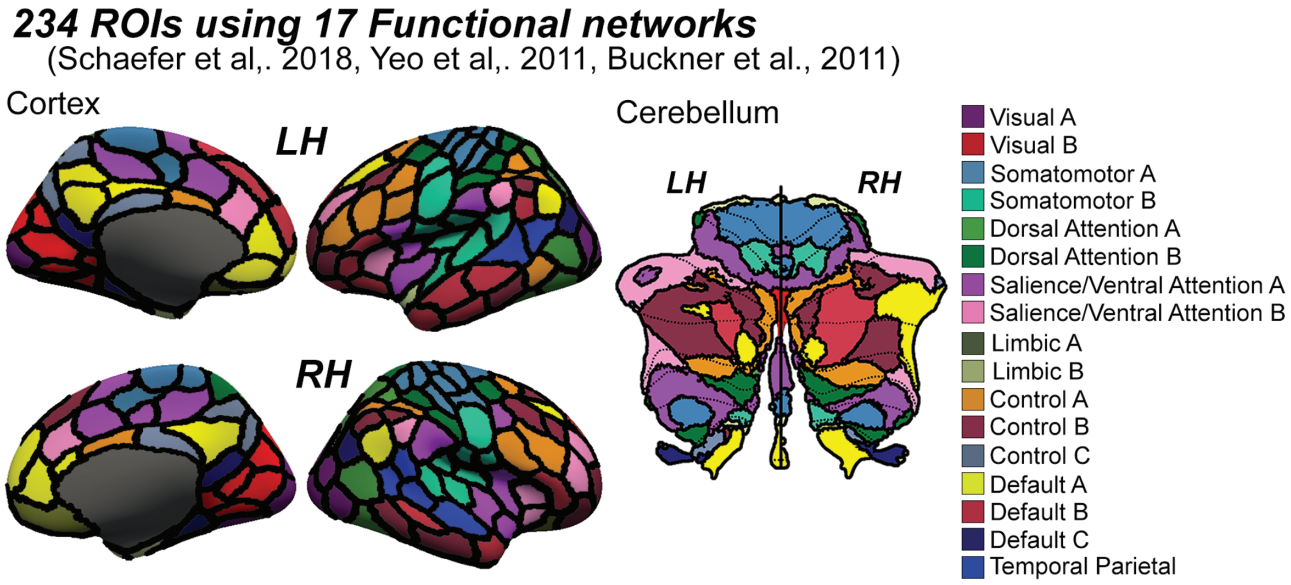

Figure 2. Fine-parcellated maps composed of 204 ROIs of cerebral cortex and 30 ROIs of cerebellum based on functional connectivity of 17 networks [48–50]. ROI, region of interest; LH, left hemisphere; RH, right hemisphere.

continuous variables and Fisher's exact tests for categorical variables with Bonferroni correction for multiple comparison were used. Network-based statistic (NBS) toolbox was used to statistically analyze connectivity matrices [51]. Between-group difference was performed to analyze the difference of the FC between healthy subjects and OSA patients, while correcting for age, as age was included as a covariate variable. Additionally, we made a subgroup of OSA composed of 53 age-matched patients with healthy subjects, then compared FC and neuropsychological scores with correct age difference between two groups. The threshold of $p < 0.05$ was set at false discovery rate (FDR) to correct for multiple comparisons. For the functional connections that showed significant group differences, we analyzed the effect of the interaction between groups (healthy, OSA) and clinical information (PSG parameters, composite scores of NP tests) to examine whether the associations between FC and clinical information differs between healthy subjects and OSA patients. The analysis included age and BMI as covariates.

For the graph theory analysis, we further calculated network characteristics, including the clustering coefficient and the global or local efficiency based on the weighted matrix, and repeated the aforementioned statistical tests on these measurements. To quantify these network properties, we first defined the characteristic path *length* L of a network as the mean minimum number of edges between any two nodes, that is, the shortest path $L_{i,j}$. $L_{i,j}$ between nodes i and j is defined as the lowest number of edges that must be traversed to go from i to j. A node's average path length $L(i, G)$ is the average length of the shortest paths between i and all other nodes. Accordingly, the *global and local efficiency*, E, of a graph G is as follows:

$$E(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{L_{i,j}}.$$

We then computed the *clustering coefficient* using standard formulas [52]. These quantities are widely used graph-theoretical parameters to describe network topology. Clustering coefficient C_i of a given node i was defined as:

$$C_i = \frac{T_i}{k_i(k_i - 1)/2},$$

where T_i is the number of existing connections among the neighbors of node i. As k_i is the actual number of neighbors of node i (i.e. its degree), the denominator term $k_i \times (k_i - 1)/2$ quantifies the number of all possible connections among the neighboring nodes. If a node i had only one edge or no edges, C_i was set to 0. Mean network clustering C was defined as the average of C_i overall nodes.

The clustering coefficient is considered a direct measure of the network's segregation, and the efficiency is an indicator of the network's integration [53].

In addition, we assigned the cerebrum and cerebellum as two separate modules, and computed the participation coefficient, a metric explaining the diversity of intermodular connections (see the formula below) [54].

$$P_i = 1 \sum_{s=1}^{N_M} \left(\frac{k_{is}}{k_i}\right)^2,$$

where k_{is} is the number of links of node in module s, and k_i is the total degree of node i. Therefore, the participation coefficient of a node is close to 1 if its links are uniformly distributed among all modules and 0 if all its links are within its own module. The mean participation coefficient for individuals was calculated by averaging values across all nodes.

Results

Clinical and polysomnographic characteristics

Detailed clinical characteristics and polysomnographic findings between the two groups were summarized in Table 1. OSA patients were more obese and drowsier than healthy subjects. Among underlying medical diseases, hypertension and diabetes were more frequent in OSA group than in healthy subjects. In PSG tests, mean ± standard deviation AHI of OSA patients was 46.4 ± 18.5/h. Compared with healthy subjects, OSA patients had higher respiratory and total arousal index, as well as higher AHI and oxygen desaturation index (ODI; corrected $p < 0.05$). We investigated the presence of WM hyperintensity using Fazekas criteria and did not find any sign of Fazekas grades 1–3 WM hyperintensities for all subjects [55].

Neuropsychological tests

Patients with OSA showed significantly lower composite scores of verbal fluency and verbal memory (corrected $p < 0.05$). There were no differences in attention and executive function and visual memory composite scores found between the two groups. The details of the neuropsychological tests are summarized in Table 2. Depression and anxiety scores were not significantly different between the groups ($p > 0.1$). When we compared age-matched OSA subgroup ($n = 53$) with healthy subjects, OSA subgroup displays a lower mean composite score of verbal fluency

Table 1. Demographics and sleep characteristics of OSA and healthy subjects

	OSA (n = 74)	Healthy (n = 33)	P-value
Age, years	45.9 ± 10.7	39.6 ± 9.3	0.004
Men, %	100	100	
Body mass index, kg/m^2	26.9 ± 3.2	23.5 ± 1.9	<0.001*
Hypertension, *n* (%)	22 (29.7)	0 (0)	<0.001*
Diabetes, *n* (%)	14 (18.9)	0 (0)	0.005
Dyslipidemia, *n* (%)	19 (25.7)	4 (12.1)	0.134
Arrhythmia, *n* (%)	4 (5.4)	1 (3.0)	1.000
Epworth Sleepiness Scale	11.0 ± 4.9	6.2 ± 4.4	<0.001*
Beck Depression Inventory	8.0 ± 7.3	6.4 ± 6.6	0.293
Beck Anxiety Inventory	4.2 ± 6.3	4.1 ± 7.9	0.917
Night polysomnography			
Time in bed, min	421.0 ± 68.4	450.6 ± 42.9	0.024
Total sleep time, min	358.5 ± 52.7	394.2 ± 67.4	0.004
Sleep latency, min	7.5 ± 6.7	11.3 ± 10.8	0.073
REM sleep latency, min	99.7 ± 51.3	98.6 ± 52.4	0.925
Sleep efficiency, %	84.3 ± 8.4	87.2 ± 10.6	0.131
N1, %	30.7 ± 13.2	13.7 ± 5.5	<0.001*
N2, %	46.3 ± 11.9	57.2 ± 8.4	<0.001*
N3, %	3.6 ± 5.3	7.3 ± 7.9	0.017
REM, %	19.4 ± 5.4	21.8 ± 4.4	0.029
AI, /h	38.4 ± 16.0	15.0 ± 5.6	<0.001*
Respiratory AI, /h	32.8 ± 17.4	3.1 ± 3.1	<0.001*
WASO, min	60.6 ± 36.4	45.2 ± 38.2	0.051
Apnea–hypopnea index, /h	46.4 ± 18.5	3.3 ± 3.8	<0.001*
Lowest SpO2, %	79.7 ± 8.7	91.5 ± 4.1	<0.001*
Oxygen desaturation index, /h	39.5 ± 18.8	3.6 ± 4.0	<0.001*

OSA, obstructive sleep apnea; REM, rapid eye movement; WASO, wake time after sleep onset; AI, arousal index.
*Statistically significant after Bonferroni adjustment for multiple comparisons (20 two-tailed *t*-tests, $p < 0.05/24 = 0.0021$).

Table 2. Neuropsychological test scores for OSA and healthy subjects

	OSA (n = 74)	Healthy (n = 33)	P-value
Attention and executive function composite score	−0.09 ± 0.61	0.18 ± 0.63	0.044
Digit span, forward	9.6 ± 1.8	10.1 ± 1.9	
Digit span, backward	8.3 ± 2.1	8.6 ± 1.8	
Corsi block, forward	9.1 ± 1.9	10.1 ± 2.0	
Corsi block, backward	8.5 ± 1.7	8.7 ± 1.7	
Train making test A, time to completion	32.6 ± 12.2	27.3 ± 8.1	
Train making test B, time to completion	75.7 ± 27.3	64.0 ± 24.9	
Stroop tests, correct responses	107.2 ± 7.8	108.1 ± 7.0	
Verbal fluency composite score	−0.29 ± 0.77	0.58 ± 0.80	<0.001*
COWAT, phonemic	33.8 ± 12.8	46.7 ± 11.5	
COWAT, semantic	38.2 ± 7.7	45.1 ± 8.9	
Verbal memory composite score	−0.21 ± 0.78	0.41 ± 0.76	<0.001*
CVLT, total	53.3 ± 11.3	59.9 ± 9.4	
CVLT, short	11.4 ± 2.4	13.1 ± 2.6	
CVLT, long	12.1 ± 2.6	13.9 ± 2.2	
CVLT, recognition	14.8 ± 1.4	15.4 ± 0.8	
Visual memory composite score	−0.08 ± 0.78	0.16 ± 0.69	0.153
RCFT, copy	34.4 ± 1.5	34.4 ± 1.7	
RCFT, immediate	22.0 ± 6.8	24.6 ± 5.7	
RCFT, delayed	21.4 ± 6.6	23.8 ± 5.7	
RCFT, recognition	20.4 ± 2.4	20.8 ± 1.8	

OSA, obstructive sleep apnea; COWAT, controlled oral word association test; CVLT, California verbal learning test; RCFT, Rey complex figure test.
*Statistically significant after Bonferroni adjustment for multiple comparisons (4 two-tailed *t*-tests, $p < 0.05/4 = 0.0125$).

and verbal memory than healthy subjects (Supplementary Table S1).

The FC differences between OSA and healthy subjects

Figure 3 and Table 3 show the FC differences between OSA and healthy subjects. Compared with the healthy group, OSA subjects showed significantly decreased connectivity only for the between-network connections that link two different functional networks (FDR corrected: $p < 0.05$). These were cerebrocerebellar connections that included the links from the cortical regions of the dorsal attention, somatomotor, temporal parietal, and visual networks with the cerebellar regions of the dorsal attention, salience, temporal parietal, and visual networks of both hemispheres. Compared with healthy subjects, OSA patients also showed increased FC in the cortical between-network connections that linked the prefrontal regions of the control network with the prefrontal and temporal region of DMN of left hemisphere. When we compared age-matched OSA subgroup ($n = 53$) with healthy subjects, all the originally significant regions remain significant except the connection between control network and DMN in prefrontal region (Supplementary Table S2).

Relationship between FC and polysomnographic parameters

We further analyzed the regional connections (shown in Figure 3) that showed group differences in FC. We found significant effects of the interaction between *group* (healthy, OSA) and each of the *PSG parameters* including lowest SaO_2, arousal index, and AHI on regional FC changes (Figure 4). In other words, we observed the "expected" relationship in the healthy group, for which lower regional FC was associated with a higher degree of oxygen desaturation and arousal. However, this relationship was not observed in the OSA patient group for which these PSG parameters exceeded the clinically defined threshold. This pattern of interaction was found in the connection between a cortical region and a cerebellar region involved in the temporal parietal network ($p = 0.007$ in healthy group) and the connection between the temporooccipital node of the dorsal attention network and the cerebellar node of the salience network ($p = 0.030$ in healthy). For other cerebrocerebellar connections involving attention network, temporoparietal network, and somatomotor network, there were also significant effects of interaction between group and each of AHI and lowest SaO_2 (Supplementary Figure S1). However, in these regional connections, no significant correlations between PSG parameters and FC changes were observed in either healthy or OSA group.

Relationship between FC and cognitive performance

We analyzed the regional connections (Figure 3) and the neuropsychological domains (Table 2) that showed group differences. We found a significant effect of the interaction between *group* (healthy, OSA) and *verbal fluency* on a connection involved in the DMN (Figure 5, $F = 10.04$, $p = 0.002$). More specifically, we observed the "expected" relationship in the healthy group ($p = 0.048$), for which lower regional FC was associated with a lower performance score of verbal fluency. However, this relationship was reversed in the OSA group for which the verbal fluency performance was significantly lower than that of the healthy group, and greater regional FC was associated with lower performance of verbal fluency.

Comparison of network property measurement

Global network property measurement, including clustering coefficient and global efficiency, were not significantly different between the two groups, but participation coefficient of OSA patients was significantly lower than healthy subjects (Supplementary Figure S2). In the analysis of regional network property metrics, we found reduced network integration in the OSA group compared with healthy subjects, including decreased clustering coefficient of the salience network in the left cerebellum and decreased local efficiency of the salience network in the left cerebellum (uncorrected $p < 0.05$; Supplementary Figure S3A). We also analyzed relationships between regional network integration that showed the group difference found in Figure 3 and sleep parameters. We found a significant effect of the interaction between group and arousal index, and that the significant correlation of local efficiency and clustering coefficient with arousal index was observed only in the healthy group, which was similar to the patterns found in the analysis of FC (Supplementary Figure S3B).

Discussion

In the present study, we investigated whole brain FC including cerebellar connections in OSA patients using rs-fMRI. This study

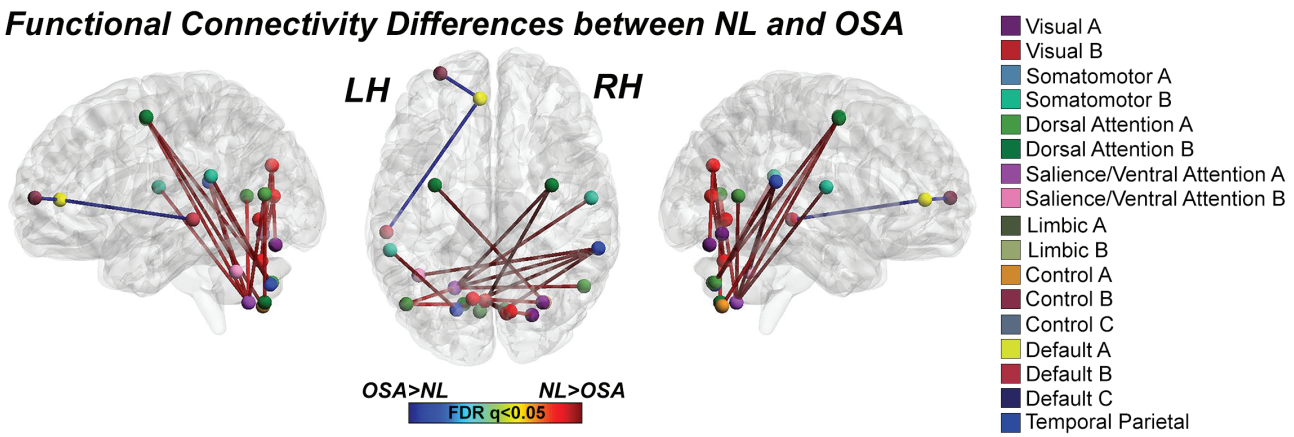

Figure 3. Altered functional connectivity (FC) in OSA subjects. Blue lines represent increased FC and red lines represent decreased FC in OSA subjects compared with healthy subjects. The color of the nodes represents the type of network. OSA, obstructive sleep apnea; LH, left hemisphere; RH, right hemisphere.

Table 3. Functional connectivity differences between patients with OSA and healthy subjects

ROI1		ROI2		t-value
OSA>NL				
L	ContB_PFClv_2	L	DefaultA_PFCm_3	−3.73
L	DefaultA_PFCm_3	L	DefaultB_Temp_4	−3.79
NL>OSA				
L	DorsAttnB_FEF_1	R	ControltA_Cerebellum	4.28
R	DorsAttnB_FEF_1	L	SalVentAttnA_Cerebellum	3.78
R	DorsAttnB_FEF_1	L	DorsAttnA_Cerebellum	3.95
R	SomMotB_S2_6	L	SalVentAttnA_Cerebellum	3.61
L	SomMotB_Aud_5	L	TempPar_Cerebellum	3.90
R	TempPar_4	L	SalVentAttnB_Cerebellum	4.16
R	TempPar_4	L	SalVentAttnA_Cerebellum	3.88
R	TempPar_4	L	TempPar_Cerebellum	4.37
R	TempPar_4	R	DorsAttnA_Cerebellum	3.75
L	DorsAttnA_TempOcc_3	L	SalVentAttnA_Cerebellum	3.75
L	VisB_ExStrSup_2	R	VisA_ExStr_1	3.74
R	VisB_ExStrSup_5	L	VisB_Cerebellum	3.95
R	VisB_ExStrSup_3	L	VisB_Cerebellum	3.98
R	VisB_ExStrSup_5	R	VisA_Cerebellum	3.43
L	DorsAttnA_TempOcc_3	L	DorsAttnB_Cerebellum	3.40
R	DorsAttnA_TempOcc_2	L	SalVentAttnA_Cerebellum	3.32

DorsAttn, dorsal attention; SalVentAttn, salience (ventral attention); SomMot, somatomotor; TempPar, temporal-parietal; Vis, visual; PFClv, lateral ventral prefrontal cortex; PFCm, medial prefrontal cortex; Temp, temporal; FEF, frontal eye field; S2, secondary somatosensory cortex; Aud, auditory; TempOcc, temporal occipital; ExStrSup, extrastriate superior; ExStr, extrastriate.

demonstrated that OSA patients display decreased FC involving multiple functional networks related to attention, somatomotor, visual, and language function, particularly in cerebrocerebellar connections. Furthermore, we found a different pattern of correlation of altered FC with sleep/cognition parameters between OSA and healthy subjects. Altered FC in OSA further led to topological changes in the integration of the cerebellar network.

The FC differences between OSA and healthy subjects

Comparing FC between OSA and healthy subjects, the most propounding pattern was decreased FC in cerebrocebellar between-network connections in OSA patients. These connections included cerebellar regions of dorsal attention, salience, temporoparietal, and cortical regions of dorsal attention, somatomotor, temporoparietal, and visual networks. Previous studies on resting-state FC in OSA subjects found local FC alterations in multiple brain regions of several networks, including medial prefrontal cortex, dorsolateral prefrontal cortex (DLPFC), postcingulate cortex (PCC), sensorimotor cortex, hippocampus, cingulate, insula, and basal ganglia [21, 23, 25, 26, 29]. However, most of the previous studies investigated only a limited number of networks, without including the cerebellum. One study analyzed whole brain FC including the cerebellum, using a functional atlas consisting of 90 cerebral regions (45 sites in each hemisphere) and 26 cerebellar areas [25]. In the present study, we partitioned the brain into 234 regions including 200 cortical parcels and 34 parcels of cerebellum, which were also grouped to define 17 functional networks for better interpretation. Therefore, we were able to find a more detailed pattern of cerebral, cerebellar, and cerebrocerebellar connectivity in relation to OSA.

The cerebellum was considered to be involved mainly in motor coordination, but recent research revealed that the cerebellum plays more than one role; it is also involved in multiple functional domains including sensorimotor processing, emotional regulation, learning, and attention through extensive cerebrocerebellar connections [30, 56–59]. Moreover, there is increasing evidence for cerebellar involvement in various neurologic and psychiatric conditions including Alzheimer's disease, frontotemporal dementia, Parkinson's disease, autism, and mood disorders [60–63]. The role of cerebellum in sleep and its relation to sleep disorders still remains unclear, but several studies suggest that the cerebellum participates in the regulation of sleep–wake cycles and generation of rapid eye movement (REM) sleep atonia [64]. Previous fMRI studies demonstrated that cerebellar activity increases during the slow wave sleep that co-occurs with slow oscillations [65]. In contrast, reduced resting-state FC between the cerebellum and multiple cortical regions was observed following sleep deprivation [66]. Thus it could be suggested that altered sleep structures, sleep fragmentation, and decreased slow wave sleep could be the main factors causing the disruptions to cerebrocerebellar connections found in our study in OSA subjects. Our findings were consistent with a prior study that demonstrated altered cerebrocerebellar FC in OSA [25]. The main difference in the current study's finding is only decreased FC between cerebellar and cerebral cortical nodes, in contrast to the mixed pattern of

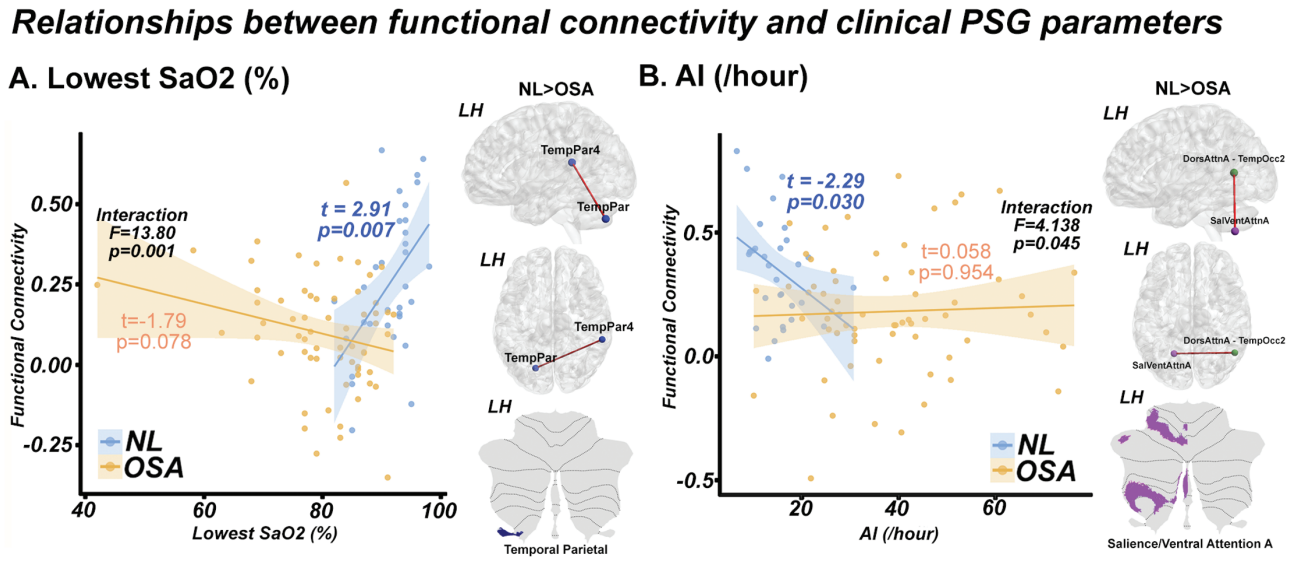

Figure 4. Correlation of functional connectivity (FC) with sleep parameters in the pooled group of OSA and healthy subjects. Significant correlation of FC with lowest SaO_2 (left) and arousal index (right) was found in the healthy group (blue clusters) whereas no such association was observed in OSA subjects (yellow clusters).

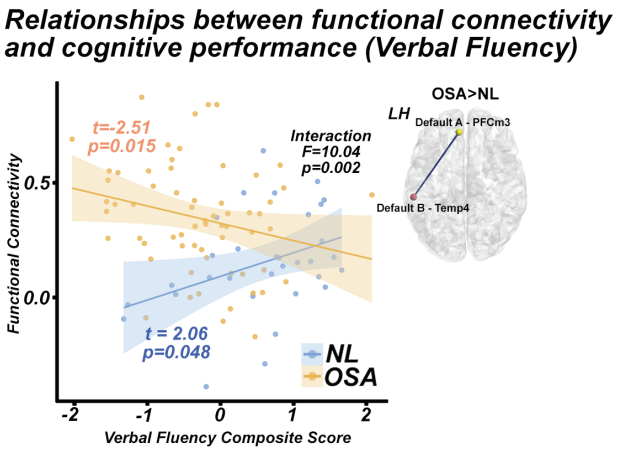

Figure 5. Correlation of functional connectivity (FC) with verbal fluency in the pooled group of OSA and healthy subjects. Significant negative correlation between FC and verbal fluency in OSA patients (yellow clusters) was observed while healthy subjects showed weak positive correlation.

increased and decreased FC of within-cerebellar connections in the previous study. In addition to the previous finding, the current finding highlights the importance of cerebrocerebellar connections underlying the pathophysiology of OSA. One recent study also demonstrated decreased FC between left cerebellum and hippocampus in OSA supporting our findings, although they investigated smaller number of subjects and analyzed only hippocampal networks compared with our study [67]. The cerebrocerebellar connectivity in OSA might be altered along with the impaired integration of cerebellar networks, which we found as lower clustering coefficient and lower network efficiency in OSA relative to healthy subjects.

In addition to alterations and impaired integration of cerebellar networks, the current study also showed increased FC in the cortical between-network connections linking prefrontal regions of the control network with the prefrontal region and temporal region of DMN. The alterations in DMN and control networks in OSA patients were extensively investigated in numerous previous rs-fMRI studies of OSA, and functional abnormalities in prefrontal regions and temporal structures have been reported in several reports [21, 23, 24, 27, 28, 68]. Some of these studies demonstrated correlations of these FC alterations with severity of OSA or cognitive impairments [21, 23, 27].

Although the exact pathomechanisms of disruption to cerebrocerebellar connections and alterations of connections between cortical DMN and control networks in OSA patients remains unknown, it is hypothetically attributed to, or related to, degenerative changes of brain structure and regional cerebral hypoperfusion in OSA. Regional decrease in GM volume and disrupted WM integrity in the cerebellum has been reported in previous studies, [7, 8] as well as regional hypoperfusion in multiple areas in the cerebellum [69–71]. Furthermore, regional structural and cerebral blood flow changes in frontoparietal areas have been reported in numerous voxel-based morphometry, diffusion tensor imaging, and perfusion MRI studies in OSA, and these changes largely overlapped with areas of the DMN and control network, which largely supports this hypothesis. The causal relationship between these structural, cerebral blood perfusion, and functional network disruptions is yet unclear. Further longitudinal studies of OSA subjects using multimodal imaging may clarify this causality and provide insights into the related degenerative process of the brain in OSA.

Association of brain FC with polysomnographic parameters and cognitive performance

Sleep fragmentation and hypoxia were considered primary pathomechanisms of OSA, which may lead to neurodegeneration through oxidative stress, inflammation, and cerebrovascular changes [3, 4]. Some studies demonstrated significant correlations between FC in multiple areas including DLPFC, amygdala, and cerebellum, and parameters of hypoxia, such as AHI and ODI in OSA patients [23, 28]. We found a significant interaction between group (healthy, OSA) and sleep parameters including lowest SaO_2, arousal index, and AHI on regional FC changes, suggesting that the spontaneous association between

lower oxygen saturation, more arousal, or a greater number of apnea/hypopneas and lower FC, which is established in healthy subjects, is not observed in patients with OSA. The possible explanation is that the intermittent hypoxias and sleep fragmentations led by the apneas and hypopneas that occur more frequently than the clinically defined cutoff for OSA might modify functional network topology, like the decreased network integration seen in our results, consequently resulting in an impaired association between sleep parameters and connectivity.

A similar pattern of interaction was observed between group and verbal fluency on a connection involved in the DMN, where the positive correlation between DMN connectivity and performance of verbal fluency was found only in healthy subjects. In OSA subjects, by contrast, we found a significantly negative correlation of the DMN connectivity with verbal fluency, implying increased FC in this region was related to impaired verbal fluency in these subjects. Increasing evidence implicates aberrant activities of the DMN, seen as abnormally large FC, associated with cognitive impairments in various neuropsychiatric disorders, such as mild cognitive impairment, Alzheimer's disease, and depression [72–74]. Among fMRI studies of OSA, Prilipko et al. found that OSA patients displayed hyperactivation of the DMN during working memory tasks, suggesting that inhibition of the resting activity in the DMN plays an important role in cognitive impairment [22]. This hypothesis is supported by our finding regarding greater DMN connectivity linked with decreased verbal fluency, as well as the study by Li et al., which found a negative association between FC of the PCC-right hippocampus and delayed memory scores in OSA [21].

Topological changes of brain functional networks

Few studies have reported decreased integrations of brain functional networks in relation to OSA [25, 75, 76]. In the present study, we did not find changes to global clustering coefficiency and global efficiency despite of alterations of FC in various connections in OSA group. In the analysis of FC, most differences in the two-group comparisons were found as lower connectivity of cerebrocerebellar connections in OSA patients compared with healthy subjects. On the other hand, only two connections within the cerebrum showed higher connectivity in the OSA patient relative to healthy subjects. Our analysis of the network metrics used in the original manuscript did not consider the observed pattern of "changes in the specific connectivity between the cerebrum and cerebellum," therefore resulting in a lack of sensitivity to group difference. This is why we assigned the cerebrum and cerebellum as two separate modules and computed the participation coefficient. In contrast to comparison of other metrics, OSA patients showed lower participation coefficient than healthy subjects, resulted from decreased intermodular connectivity (cerebrocerebellar connections) in the patient group.

In comparison of local network parameters, we found decreased local efficiency and decreased clustering coefficient of the salience network located in the left cerebellum. The salience network plays an important role in the detection and screening of emotional stimuli, and has been known to be affected by OSA and insomnia [77]. Our finding of altered regional network topology in the cerebellum may indicate a weakened-hubness role of this functional network. We also found decreased FC in cerebellar regions connecting the salience network with cerebral cortical regions of other functional networks. Overall, this suggests that hubs in the cerebellar network weakened following OSA might further lead to abruptly relaying functional activities through the cerebrocerebellar connections.

Limitations and strengths

We acknowledge some limitations in our study. Most of all, we should have considered the heterogeneity between OSA patients and control group. The BMI of the healthy and OSA subjects in the current study significantly differ, which might have affected functional network connection and cognitive performance. Although the statistical methods adopted here took this into account by adjusting the effects of BMI, the possible residual effects may remain and need further investigation. OSA patients were older than healthy subjects in this study, though the difference is not statistically significant after Bonferroni correction. To mitigate these concerns, we further performed a separate analysis on a subgroup of our OSA patients, mean age of which was matched with that of healthy subjects, and demonstrated the similar pattern of alterations in network disruption and impairment in cognitive performance for OSA patients. Furthermore, we examined the presence of common vascular risk factors in our study cohort. We found a significantly higher prevalence in OSA patients for hypertension and diabetes than controls. We then assessed whether each of hypertension and diabetes altered FC within the OSA group. We thus dichotomized our OSA group with respect to the presence of each symptom and found no FC difference between two OSA subgroup with and those without hypertension and diabetes.

Another limitation is that our study included only male OSA patients for sample collection and homogeneity. Thus, future investigations with different populations are still needed. Lastly, we analyzed the brain connectivity with 234 regions, including cortical and cerebellum regions. However, this excluded the subcortical GM regions that are important for the relationship with the cerebellum, such as the thalamus and basal ganglia. Further research is required to clarify the role of these subcortical areas in the alteration of FC following OSA.

The strength of the study is our analytic framework that allowed us to investigate the whole brain FC of multiple functional networks using fine parcellation of brain functional areas including the cerebellum. It enabled us to identify the novel pattern of alterations in cerebrocerebellar functional connections for OSA patients. Notably, cerebrocerebellar connectivity has been less highlighted in previous OSA studies. Another strength of the current study is that PSG data were available for all healthy subjects as well as OSA patients, excluding subjects with potentially underdiagnosed sleep disorders. Availability of PSG data further allowed us to analyze the association between FC and quantitative sleep parameters in both OSA and healthy subjects. Indeed, this analysis revealed distinctive patterns of FC correcting for PSG parameters between two groups. Lastly, neuropsychological tests representing several important cognitive functional domains were performed for all the subjects included in the study. Thus, we could assess the relationship between FC and each domain of cognitive functions.

Conclusion

Treatment-naive, male OSA subjects showed altered FC in resting state in multiple brain regions, particularly in cerebrocerebellar connections. OSA-related connectivity alterations further led to disruptions in global and local network integration. The association between FC and PSG parameters found in our study explains that FC alterations in OSA are likely due to sleep fragmentation and hypoxia, possibly through the structural changes and impaired blood perfusion in the brain. Changes in networks playing an important role in sleep, such as the DMN, were associated with cognitive performance decline (less verbal fluency) in OSA subjects. These findings may provide new insight into the pathophysiology underlying OSA and the cognitive impairment following OSA.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Disclosure Statements

None declared.

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