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ORIGINAL RESEARCH

Altered Density of Resting-State Long- and Short-Range Functional Connectivity in Patients with Moderate-to-Severe Obstructive Sleep Apnea

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Purpose: This study is to evaluate the altered number of functional connection (s) in patients with obstructive sleep apnea (OSA) by functional connectivity density (FCD), to investigate its relationship with cognitive function, and to explore whether these features could be used to distinguish OSA from healthy controls (HCs).

Methods: Seventy-six OSA patients and 72 HCs were included in the analysis. All participants underwent resting-state functional magnetic resonance imaging scan. Subsequently, intergroup differences between long-and short-range FCD groups were obtained in the Matlab platform by using the degree centrality option with a 75 mm cutoff. The partial correlation analysis were used to assess the relationship between the altered FCD value and clinical assessments in OSA patients. The FCD values of the different brain regions were used as classification features to distinguish the two groups by support vector machine (SVM).

Results: Compared to HCs, OSA patients had decreased long-range FCD in the right superior frontal gyrus (SFG), right precuneus, and left middle frontal gyrus (MFG). Simultaneously, increased long-range FCD in the right cingulate gyrus (CG). Meanwhile, the short-range FCD were decreased in the right postcentral gyrus (PoCG), right SFG, left MFG, and right CG. The short-range FCD values of the right PoCG were correlated with the Montreal Cognitive Assessment scores in OSA patients. SVM analysis showed that FCD in differential brain regions could differentiate OSA patients from HCs.

Conclusion: Long- and short-range FCD values in different brain regions of OSA patients may be related to cognitive decline, and also be effective in distinguishing OSA patients from HCs. These findings provide new perspectives on neurocognition in OSA patients.

Keywords: cognitive function, functional magnetic resonance imaging, functional connectivity density, obstructive sleep apnea

Introduction

Obstructive sleep apnea (OSA) is one of the most common sleep disorders, with the symptoms of upper airway collapse, intermittent hypoxemia, apnea and sleep fragmentation.[1] It can lead to disrupted sleep architecture, daytime sleepiness, various complications, and reduced overall quality of life.[2] A global study on OSA prevalence revealed rates ranging from 9% to 38%, with adult males having a higher prevalence than adult females.[3] OSA can also cause psychiatric symptoms and cognitive impairment such as depression, anxiety and cognitive decline.[4,5] Despite extensive investigations, the exact neural mechanisms responsible of cognitive dysfunction in patients with OSA remain unclear.

In the past decade, the rapid development of functional magnetic resonance imaging (fMRI) techniques has provided crucial insights into the central mechanisms of neurocognitive deficits in patients with OSA. Techniques such as regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), and percent amplitude of fluctuation (PerAF)[6–8] have been instrumental in studying changes in brain region activity in patients with OSA. However, these techniques have limitations in assessing interactions or functional integration between brain regions. It is well known that neurocognitive deficits in patients with OSA may be mediated by damage to multiple brain regions.[9,10] Many studies

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have investigated abnormal functional integration in patients with OSA using resting-state functional connectivity (FC), and abnormal FC has been found in several important brain regions were found in patients with OSA.[11–15] However, these studies used seed-based FC analyses, which is more region-specific and hypothesis-driven and may miss critical unpredictable results. Functional connectivity density (FCD) has been proposed as a data-driven method based on graph theory that does not require any prior assumptions or seed point selection, to describe the topology of a brain network to reflect the communication of the region with other regions of the brain;[16,17] it was able to identify differences in the number of connections in brain networks from a whole-brain perspective. FCD provides more information about brain functional changes compared to traditional FC methods. This method characterizes cortical and subcortical brain regions by resting-state networks associated with long- and short-range FCD regions. It provides a comprehensive analysis of connectivity patterns and their alterations across different spatial scales. In recent years, many studies have been used FCD map on conditions such as diabetes, chronic migraine and Alzheimer's disease, which showed that FCD can be used to explore FC aberrations from a new perspective to reflect the mechanism and compensation for cognitive function.[18–20] However, the differences in the number of functional connections in the brain network and the comprehensive functional network abnormalities are currently unknown in patients with OSA, so we intend to investigate altered FCD patterns in patients with OSA using FCD map, assess their association with cognitive impairment.

Machine learning is used in the area of predictive classification of neuroimaging diseases. Support vector machines (SVMs) have shown excellent performance in classification tasks by seeking two classification hyperplanes with a maximum margin and using kernel tricks to handle nonlinearity.[21] Many neurodegenerative diseases use the classification metrics of SVM classifiers to distinguish patients from HCs, obtaining good classification performance, such as Parkinson's,[22] Alzheimer's disease.[23] Given the effectiveness of SVMs in clinical diagnosis, we attempted to use SVMs based on the FCD data to distinguish patients with OSA from HCs.

In the present work, we hypothesized that long- and short-range FCD is altered in some brain regions in OSA patients. The FCD values for changes in differential brain regions are not only correlated with cognitive status, but also can be distinguished as a potential biomarker from the normal population. To test these hypotheses, long- and short-range FCD were calculated separately using the degree centrality option characterized by 75 mm. Then, we explored the relationship between the FCD values in these disparate brain regions and the clinical characteristics of patients, including their neurocognitive function. Finally, we identified whether the abnormal long- and short-range FCD values in differential brain regions are distinguishable between patients with OSA and HCs by the SVM classifier. These findings may help clinicians to assess whether such patients are at risk for cognitive decline in the future. Further, potential imaging markers for distinguishing the patients with OSA and HCs were proposed.

Materials and Methods

Participants

This study recruited 76 newly diagnosed patients with moderate or severe OSA from the Department of Otorhinolaryngology or the Sleep Monitoring Unit of the Department of Respiratory Medicine at the First Affiliated Hospital of Nanchang University. The control group of 72 HCs was healthy, education-and age-matched volunteers from the community postings. The inclusion criteria for patients with OSA following the American Academy of Sleep Medicine (AASM). The criteria were (1) male; (2) 18–65 years of age; (3) Apnea Hypopnea Index (AHI) ≥15 episodes/hour; and (4) right-handed. The exclusion criteria were as follows: (1) other medical conditions, such as presence of sleep disorders other than OSA; cardiopulmonary disease, central nervous system disease, hypothyroidism, renal or hepatic disease, history of diabetes or cancer, and previous upper airway surgery, lung surgery, or treatment for snoring; (2) absence of structural abnormalities on MRI and visual inspection of the brain; (3) alcoholism or current use of psychotropic drugs or abuse of illicit drugs; (4) poor quality of imaging data; and (5) MRI contraindications (such as, claustrophobia, devices). Three patients with OSA and one HC were subsequently excluded. This study was approved by the Ethical Review Committee of the First Affiliated Hospital of Nanchang University [2020(12-94)] and complied with the principles of the Declaration of Helsinki. All the patients provided informed consent.

Polysomnography (PSG)

To confirm the diagnosis of OSA, all participants had to undergo a nocturnal PSG using the Respironics LE series of physiologic monitoring systems (Alice 5 LE, Respironics, Orlando, FL, USA).[24] Clinical scale tests and fMRI assessments were performed the day after the PSG assessment. A sleep specialist guided the patient through a sleep test, analyzing and interpreting the recorded results for reliability. All participants were required to not consume beverages containing alcohol, tea, or coffee before PSG, and the test was performed from 10 p.m. to 6 a.m. the following day. Concurrently, jaw-chin electromyogram, electrocardiogram, two-lead electrooculogram, standard electroencephalogram, and oxygen saturation (SaO_2) were examined in all participants. Various sleep parameters were recorded, including total sleep time, mean arterial oxygen saturation ($mSaO_2$), awakening, and respiratory events. OSA was defined as at least 30 episodes of apnea in adults during a 7-hour nocturnal sleep period, with cessation of oro-nasal airflow for at least 10s during each episode. AHI was defined as the total number of apnea and hypoventilation events per hour, as an indicator of the severity of the sleep apnea. Based on the AASM definition of OSA, the AHI was used to define the severity grading of OSA,[25] with AHI of 5–15/h, 16–30/h, and > 30/h classified as mild, moderate, and severe OSA, respectively.

Clinical and Neuropsychological Measures

Clinical data collected included the arousal index, oxygen desaturation index, total sleep time, sleep staging, and minimum oxygen saturation. The results of neuropsychological tests for patients with OSA and HCs, such as those of the Montreal Cognitive Assessment Scale (MoCA, Chinese version) and the Epworth Sleepiness Scale (ESS, Chinese version) were assessed. Cognitive performance was evaluated with MoCA items testing the domains of executive function, attention, naming, language, memory, abstraction, and orientation. The MoCA scale is scored out of 30, with scores below 26 indicating cognitive impairment. If the number of years of education is less than 12, an additional point is added to adjust for educational bias.[26] The ESS prompts participants to assess the likelihood of falling asleep in eight different situations on a probability scale of 0–3. The ESS was used to assess the possibility of sleep. Scores on this scale range from 0–24, with values greater than 6 indicating sleepiness, values greater than 11 indicating excessive sleepiness, and values greater than 16 indicating dangerous sleepiness.[27] All assessments were conducted by an experienced physician with no clinical information about the participants. All the tests were performed uniformly in the same manner.

MRI Data Acquisition

MRI scans were completed using a 3.0 T Magnetic Resonance Imaging System (Siemens, Munich, Germany) to acquire data, in the First Affiliated Hospital of Nanchang University, China. During the scanning process, we used foam to minimize artificially induced head movements and earplugs to minimize noise interference from the scanner. Participants were instructed to relax, remain still, maintain a supine position with the head in a neutral position and eyes closed, and to avoid or minimize active thinking and falling asleep. First, the participants were scheduled for conventional T1-weighted imaging [repetition time (TR) = 1900 ms, echo time (TE) = 2.26 ms, thickness = 1.0 mm, flip angle = 9°, field of view (FOV) = 250 mm×250 mm, with 176 sagittal slices] to exclude those with obvious structural brain lesions. Second, we used a gradient recalled echo planar imaging pulse to obtain rs-fMRI data (TR = 2000 ms, TE = 30 ms, thickness = 4 mm, gap = 1.2 mm, flip angle = 90°, FOV = 230 mm×230 mm, scanning time 8 minutes); each functional run included 240 volumes, and 30 axial slices to cover each brain volume.

fMRI Data Preprocessing

Initially, using MRIcro software, all the MRI images were checked and defective images were removed. The Data Processing and Analysis for Brain Imaging (DPABI V6.2, http://rfmri.org/dpabi) toolbox and Statistical Parametric Mapping software package version 12 were used to preprocess the functional images. During processing, each participant's first 10 time points were discarded to eliminate the effects of MRI scanner noise and magnetic saturation. The remaining 230 volumes were corrected for slice timing to the first timepoint for 3D head motion corrections. Participants were included using the head movement criteria of maximum rotation (x, y, z) < 2° and maximum directional displacement (x, y, z) < 2 mm. Thereafter, the realigned functional data were co-registered with their respective high-

resolution T1-weighted structural images and then spatially normalized to the standard Montreal Neurological Institute space, with a resampled voxel size of 3 × 3×3 mm^3, having regressed out the nuisance variables. Finally, temporal band-pass filtering (0.01–0.08 Hz) was used to minimize the physiological noise of high-frequency components and to remove magnetic field drifts from the scanner. Ultimately, two OSA cases were excluded based on head movement criteria.

Resting-State FCD Calculations

Long- and short-range FCD calculations were performed on Graph Theory Network Analysis (Gretna, http://www.nitrc.org/projects/gretna/). This study followed the method previously described by Tomasi and Wavelow,[16,17] using a program to compute the FCD for each voxel. The results of these computations for each voxel comprise the global FCD. According to a previous study,[28] effective FC within the short-range FCD region means connectivity within a specific 75 mm anatomical distance. Conversely, the long-range FCD is equivalent to the difference between the global FCD and short-range FCD.[29] We first rescaled the long- and short-range FCD plots for each data element, and additionally converted them to z-scores using Fisher's r-to-z transformation, to obtain normally distributed results. Finally, the normalized FCD data were spatially smoothed using a Gaussian kernel based on the width at a half-maximum of 6 mm. The number of functional connections between voxels was assessed using Pearson's linear correlation, as recommended by the FCD map developers. The correlation coefficient for a significant association between two voxels is $r > 0.6$. This threshold, and the internal script described above, are the best methods for calculating FCD.[30] Therefore, we used a threshold of $r = 0.6$ to calculate FCD in this study.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of continuous variables in the clinical data. The data of the control and OSA groups were statistically analyzed by independent sample *t*-tests using the IBM Statistical Package for the Social Sciences V 26.0 statistical software (Armonk, NY, USA). First, we determined the spatial distribution of FCD between the two groups of participants by a one-sample *t*-test. Body mass index (BMI), age, and years of education served as covariates in a two-sample *t*-test using the DPABI statistic based on MATLAB R2018 b (MathWorks, Natick, MA, USA), to test for differences in the FCD map on each voxel between patients with OSA and HCs. Multilevel comparisons were conducted using Gaussian random field theory (GRF, two-tailed, $p < 0.01$ at the voxel level and $p < 0.05$ at the cluster level). FCD differential brain regions were displayed using Brainnet software (http://www.nitrc.org/projects/bnv/) and the DPABI_V6.2 software packages. Finally, after accounting for covariates such as BMI, and age, a partial correlation analysis was performed using SPSS 26.0 to test the association between changes in FCD values in the differential brain regions and the associations between clinical variables including PSG measurements and ESS and MoCA scales. Statistical significance was determined at $p < 0.05$ and Bonferroni correction was applied correction to control for multiple comparisons between all independent variables.

Classification with SVM

In our study, we distinguished OSA patients and HCs by a SVM classifier using the FCD values in the differential brain regions of patients with OSA as a categorization feature. Subsequently, we use the Python sklearn library to implement SVM attacks, with all parameters set to default values. Thereafter, the SVM was trained by providing labeled observations with known classification results. We applied the nested leave-one-out cross-validation procedure to overcome the limitations of our sample.[31] Finally, the classifier's performance was evaluated based on specificity, sensitivity, and area under the curve (AUC). A flowchart of the study is shown in Figure 1.

Results

Demographics, Clinical Characteristics, and Neuropsychological Assessments

See Table 1 for participant demographics and details of the clinical data and neuropsychology assessments, respectively. BMI, AHI, arousal index, oxygen saturation descent index, and Stage N1 sleep were significantly higher in the OSA group than in the HC group. Conversely, Stage N3 sleep, rapid eye movement sleep, and minimum SaO_2 were significantly lower in the OSA group than in the HC group. Regarding neuropsychological assessment, patients with

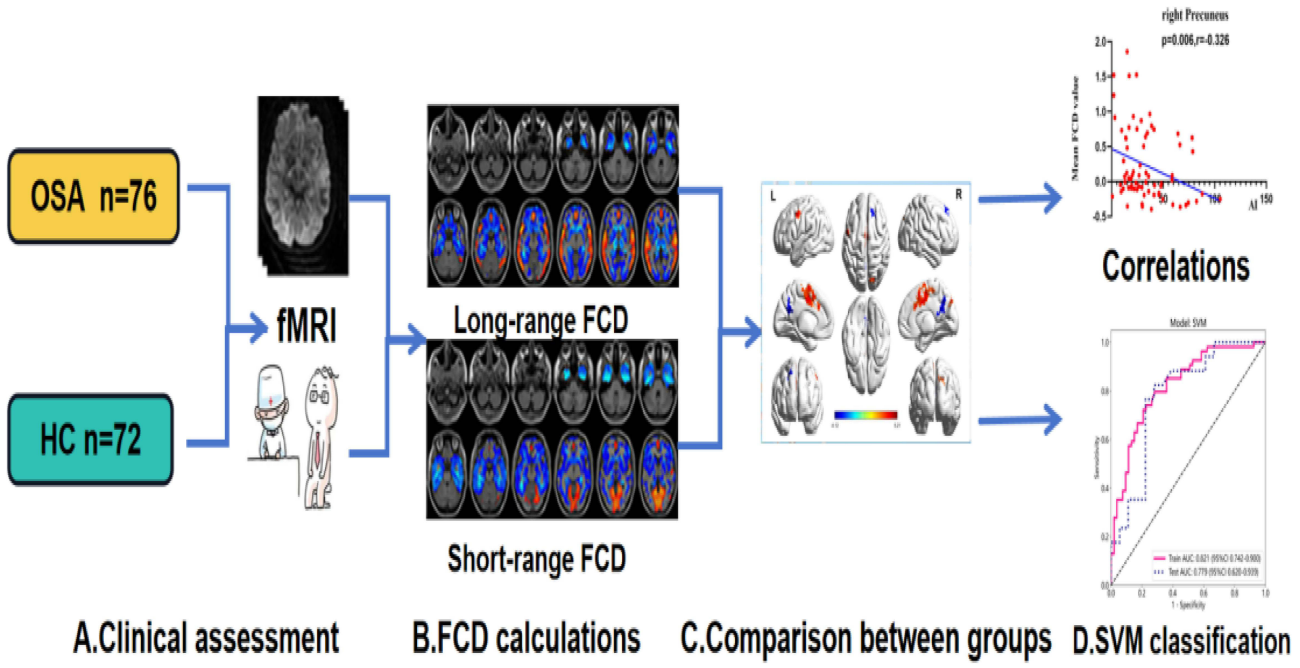

Figure 1 Flowchart of the study. A Two age- and education-matched groups of participants (76 patients with OSA and 72 HCs) underwent fMRI scans and clinical scale assessments. B The regions with abnormal long-and short-range FCD were explored in the Matlab platform with a threshold of 75 mm in the OSA and HC groups, respectively. C Distribution of brain areas of FCD differences between the two groups using a two-sample *t*-test. D Correlation analyses were performed to assess the relationship between FCD values in differential brain regions and clinical characteristics and categorized using the SVM method.
Abbreviations: OSA, obstructive sleep apnea; HCs, healthy controls; FCD, functional connectivity density; fMRI, functional magnetic resonance imaging; SVM, support vector machine.

OSA had higher ESS scores and slightly lower total MoCA scores than the HC group did. However, there were no significant differences between the two groups in age, total sleep duration, Stage N2 sleep, MoCA scale naming, and attention scores ($p > 0.05$). Additionally, we classified 32 patients with OSA as having mild cognitive impairment based on their total MoCA scores, constituting 45.1% of patients with OSA (Table 1).

Table 1 Demographics, Clinical Data, Cognitive Assessment of OSA and HCs

Characteristic	OSA Patients (N=71)	HCs (N=71)	Statistics	*p*-value
Age (years)	37.8±10.7	41.1±11.0	t=−1.821	0.071
Education (years)	12.3±3.7	10.7±3.2	z=−2.862	0.004*
BMI (kg/m2)	27.0±3.4	21.0±1.7	z=−9.369	<0.001**
OSA duration (years)	11.9±6.1	/	/	/
AHI (events/hour)	51.4±20.8	2.3±1.2	z=−10.285	<0.001**
Total sleep time (min)	361.1±96.8	380.6±30.7	z=−0.096	0.924
N1 stage (%)	29.6±15.2	10.0±3.4	z=−8.661	<0.001**
N2 stage (%)	39.3±13.5	39.9±6.4	t=−0.312	0.756
N3 stage (%)	19.2±16.3	29.7±4.9	z=−5.549	<0.001**
REM (%)	11.5±10.4	20.8±6.9	z=−5.705	<0.001**
Nadir SaO2 (%)	70.7±11.6	93.1±3.6	z=−10.189	<0.001**
Mean SaO_2 (%)	92.0±4.4	96.4±2.1	z=−6.855	<0.001**
AI (events/hour)	33.4±22.9	11.6±2.9	z=−7.655	<0.001**

(*Continued*)

Table 1 (Continued).

Characteristic	OSA Patients (N=71)	HCs (N=71)	Statistics	*p*-value
ODI (events/hour)	47.3±25.0	1.8±1.2	z=−10.277	<0.001**
ESS, scores	10.9±4.4	1.4±1.3	z=−10.075	<0.001**
MoCA, scores	25.0±3.3	27.9±1.5	z=−6.159	<0.001**
MoCA: visual space and execution	3.9±0.9	4.6±0.5	z=−4.701	<0.001**
MoCA: naming	2.9±0.3	2.9±0.3	z=−0.601	0.548
MoCA: delayed memory	3.2±1.3	4,3±0.6	z=−5.792	<0.001**
MoCA: attentional function	5.0±1.3	5.5±0.5	z=−1.944	0.052
MoCA: language	2.2±0.6	2.6±0.5	z=−4.578	<0.001**
MoCA: abstract	1.6±0.5	2.0±0.2	z=−5.466	<0.001**
MoCA: orientation	5.6±1.0	5.9±0.3	z=−1.978	0.048

Notes: *p < 0.05 and **p < 0.001, which was considered statistically significant, values are presented as the mean ± standard deviation unless otherwise indicated.
Abbreviations: SaO_2<90%, percentage of total sleep time spent at oxygen saturation less than 90%. OSA, obstructive sleep apnea; HCs, healthy controls; N, number; SD, standard deviation; BMI, body mass index; AHI, apnea-hypopnea index; REM, rapid eye movement; SaO_2, oxygen saturation; AI, arousal index;ODI, oxygen desaturation index; ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment.

Spatial Distribution of FCD

The FCD map revealed similar spatial patterns in patients with OSA and HCs. Both long- and short-range FCD demonstrated extensive spatial distribution across the frontal, temporal, parietal, and limbic lobes. Moreover, short-range FCD decreased in the precuneus (PCUN) and middle frontal gyrus (MFG), whereas long-range FCD decreased in the superior temporal gyrus and superior frontal gyrus (SFG) (Figure 2).

Group Differences in FCD

To conduct group comparisons of these long- and short-range FCDs, a two-sample *t*-test was performed to reveal differences (Table 2, Figures 3 and 4). Compared with HCs, regions exhibiting decreased long-range FCDs were the SFG, PCUN, and

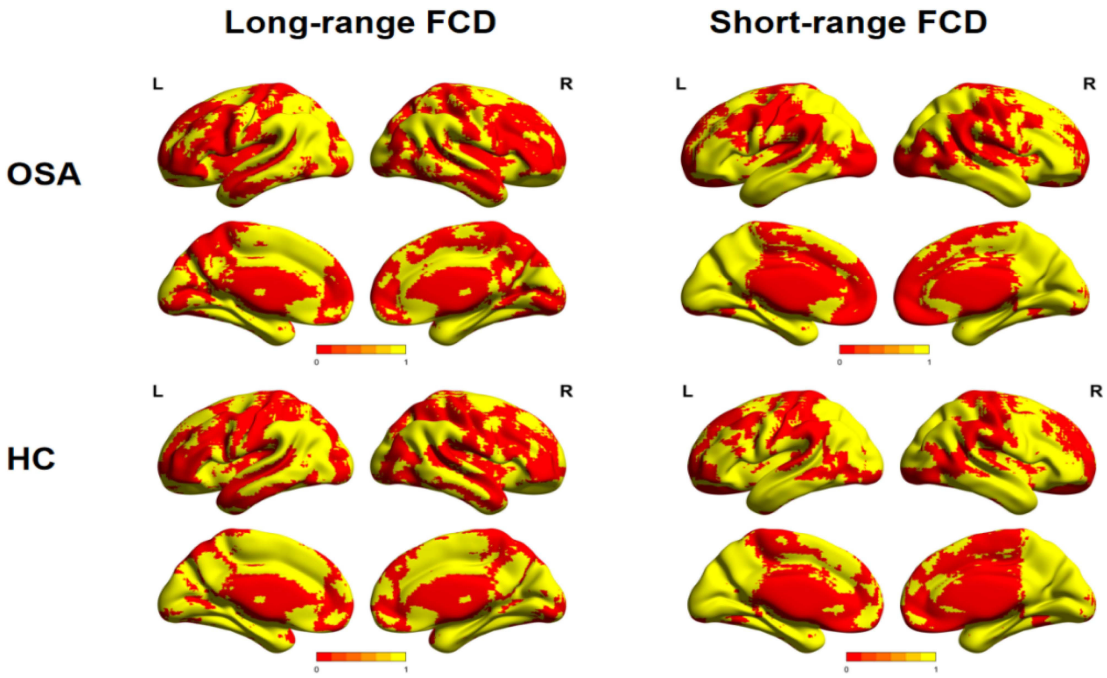

Figure 2 The long- and short-range functional connectivity density patterns of OSA patients and HCs (single sample *t*-test).
Abbreviations: FCD, functional connectivity density; OSA, obstructive sleep apnea; HCs, healthy control; L, left; R, right.

Table 2 Significant Difference of FCD Between OSA Patients and HCs

Brain Area	L/R	Cluster Size	*T-value*	MNI Coordinates of Peak Voxel		
				X	Y	Z
Long-range FCD						
Superior Frontal Gyrus	R	524	−5.006	18	51	36
Precuneus	R	501	−4.812	0	−60	24
Medial Frontal Gyrus	L	308	−4.273	−15	48	48
Cingulate Gyrus	R	460	4.661	3	−9	60
Short-range FCD						
Postcentral Gyrus	R	228	−4.061	60	−21	39
Medial Frontal Gyrus	R	284	−4.401	18	48	36
Cingulate Gyrus	R	200	−3.661	12	−51	33
Superior Frontal Gyrus	L	253	−4.258	−18	42	45

Notes: All clusters were reported with a voxel-level threshold of P < 0.01, GRF correction, and cluster-level of P < 0.05, two tailed.
Abbreviations: FCD, functional connectivity density; OSA, obstructive sleep apnea; HCs, healthy controls; MNI, Montreal Neurological Institute; L, left; R, right.

MFG, while the cingulate gyrus (CG) showed an increase in long-range FCD. Conversely, regions with decreased short-range FCD included the postcentral gyrus (PoCG), SFG, MFG, and CG (GRF correlation, voxel $p < 0.05$, cluster $p < 0.01$).

Correlations

The Figure 5 shows the correlation between FCD values of abnormal brain regions and clinical variables in patients with OSA. We found that within the discrepant long-range FCD brain regions, the right SFG and PCUN were significantly

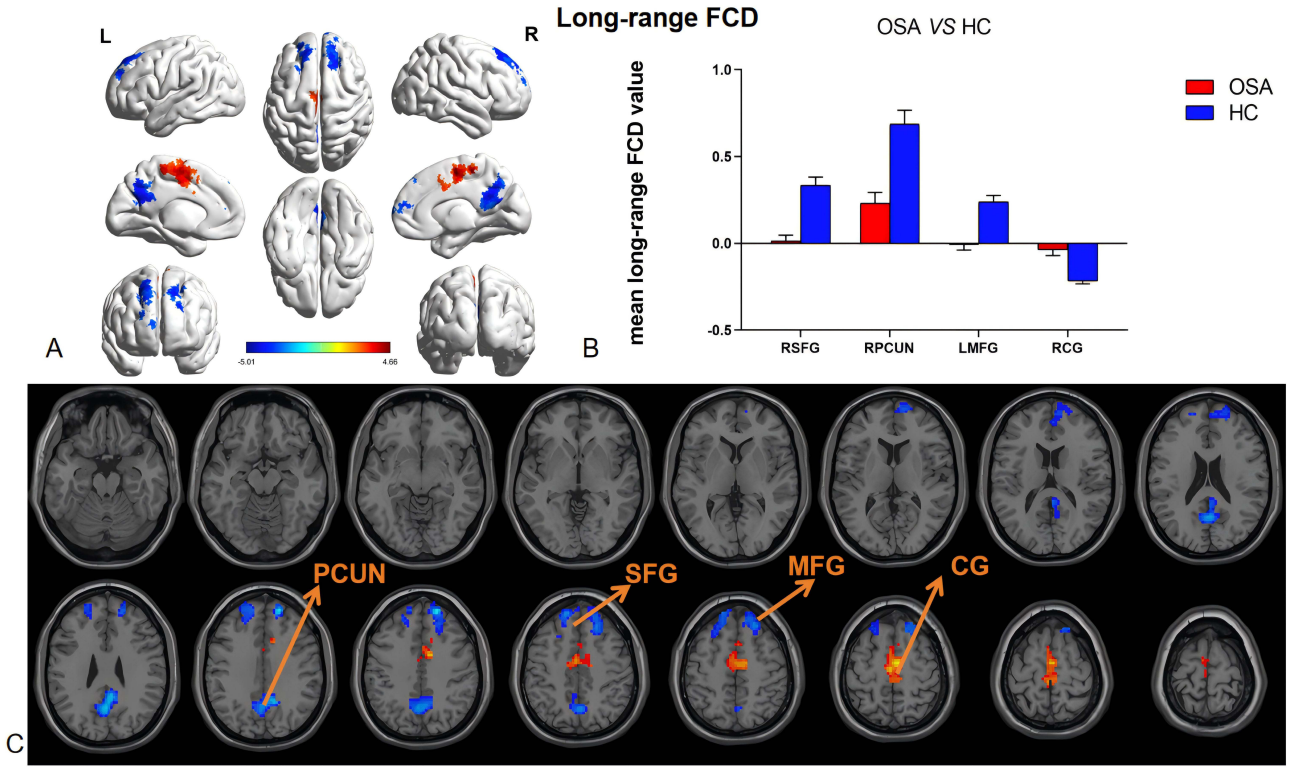

Figure 3 Brain regions with significant changes in long-range FCD in OSA contrast to HC group. (**A** and **C**) The different brain regions were observed in the right superior frontal gyrus, right precuneus, and left middle frontal gyrus, right Cingulate Gyrus in the OSA group. (**B**) The mean FCD values in the two groups. The red areas denote resting state FCD in OSA is bigger than HC, and the blue areas denote resting state FCD in OSA is smaller than HC.
Abbreviations: FCD, function connectivity density; OSA, obstructive sleep apnea; HCs, healthy controls; SFG, Superior Frontal Gyrus; PCUN, Precuneus; MFG, Medial Frontal Gyrus; CG, Cingulate Gyrus; L, left; R, right.

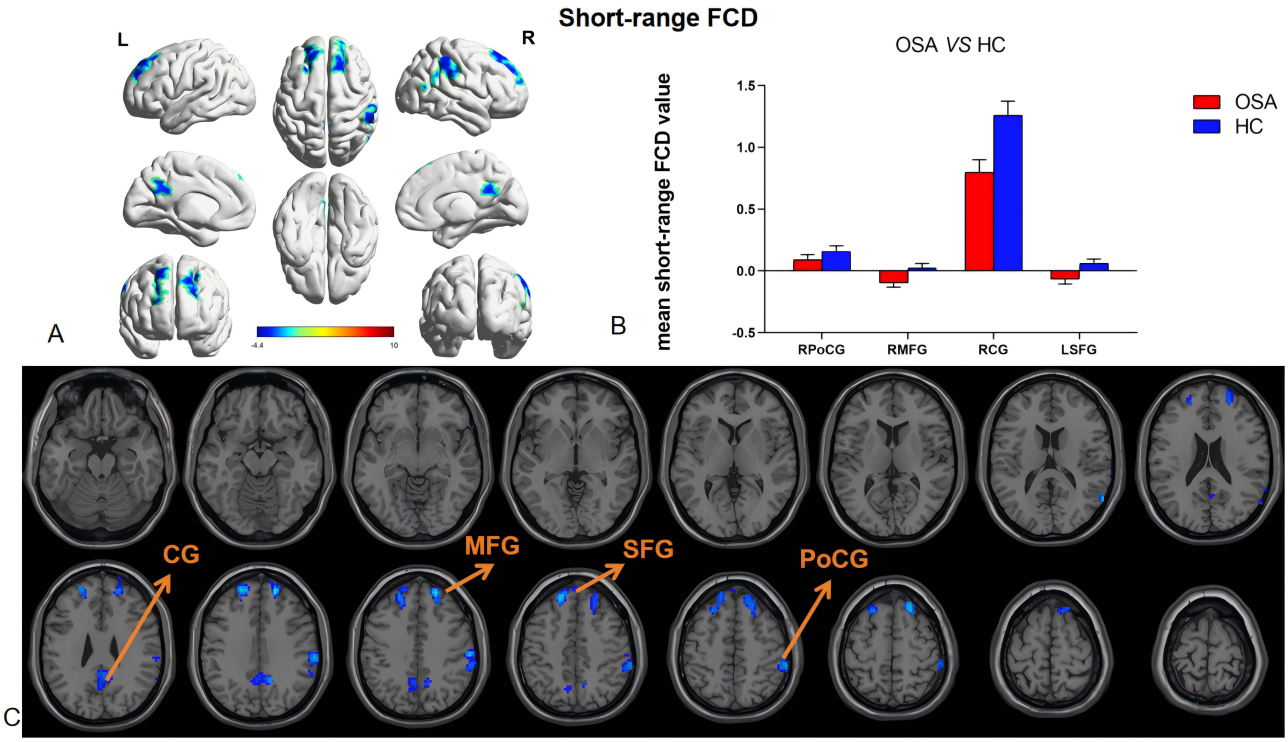

Figure 4 Brain regions with significant changes in short-range FCD in OSA contrast to HC group. (**A** and **C**) The different brain regions were observed in the right postcentral gyrus, the right superior frontal gyrus, the left middle frontal gyrus, and the right cingulate gyrus in the OSA group. The blue areas denote lower FCD brain regions. (**B**) The mean FCD values in the two groups. The blue areas denote resting state FCD in OSA is smaller than HC.
Abbreviations: FCD, function connectivity density; OSA, obstructive sleep apnea; HCs, healthy controls; PoCG, Postcentral Gyrus; MFG, Medial Frontal Gyrus; CG, Cingulate Gyrus; SFG, Superior Frontal Gyrus; L, left; R, right.

correlated with arousal index (AI) and oxygen desaturation index (ODI). Furthermore, within the discrepant short-range FCD brain regions, significant correlations existed between the right CG and AI, as well as between the right PoCG and delayed recall in the MoCA score (Figure 6).

SVM Classification results

FCD was significantly different between the OSA patients group and the HCs group. For SVM classification between the OSA and HC groups, the training set achieved a 74.8% classification accuracy (sensitivity = 75.9%; specificity = 73.6%; AUC = 82.1%; $p < 0.001$), while the test set achieved a 74.3% classification accuracy (sensitivity = 82.4%; specificity = 66.7%; AUC = 77.9%; $p < 0.001$) (Figure 7).

Discussion

To the best of our knowledge, this was the first study to investigate changes in brain activity in patients with OSA by applying FCD mapping and SVM analysis. The results showed that compared with HCs, the regions with reduced long-range FCD in patients with moderate-to-severe OSA were the right SFG, right PCUN, and left MFG, and the regions with reduced short-range FCD were the right PoCG, left SFG, and right MFG. Notably, there was an increase in long-range FCD and a decrease in short-range FCD in the right CG, which were mainly associated with the frontoparietal control network (FPCN), the default mode network (DMN), and the sensorimotor network (SMN). Additionally, short-range FCD values in the right PoCG of patients with OSA significantly correlated with MoCA scores. Furthermore, we achieved good classification performance by leveraging the FCD values of all differential brain regions as classification features between patients with OSA and HCs. Overall, these findings highlight FCD abnormalities in patients with OSA and provide valuable insights into the pathogenesis of cognitive and mood disorders.

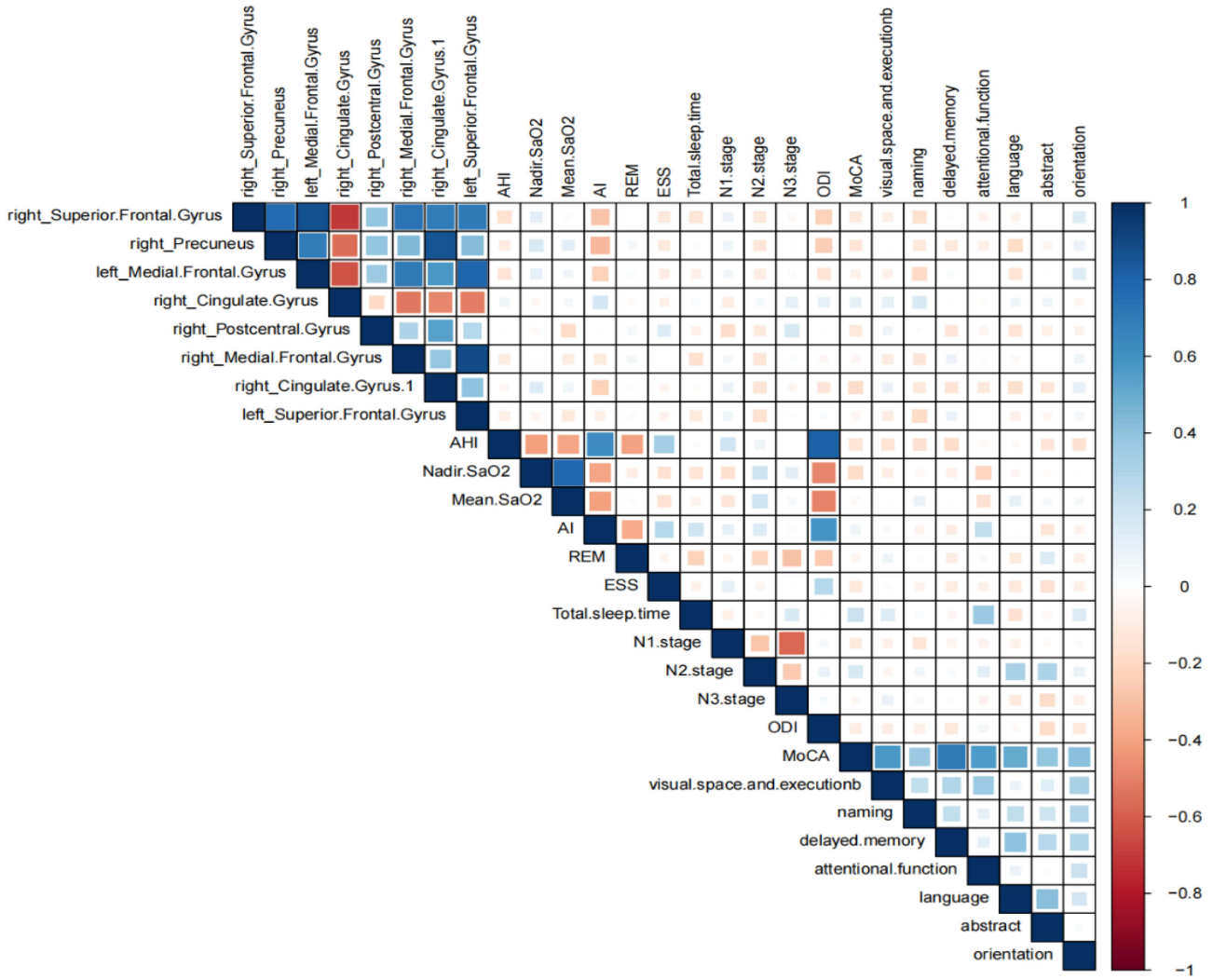

Figure 5 Correlation analysis between altered FCD values and clinical assessments and scales in OSA patients. Blue represents positive correlation, red represents negative correlation, and darker color represents stronger correlation.

Abbreviations: AI, arousal index; ODI, oxygen desaturation index; AHI, apnea-hypopnea index; REM, rapid eye movement; SaO_2, oxygen saturation; ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment.

Our study's patient group had a higher BMI than that of the HCs and included only male patients. A key risk factor for the increasing prevalence of OSA is obesity.[32] However, recent studies have shown that changes in resting-state brain activity in patients with OSA are caused by OSA rather than by obesity.[33,34] In the present study, we controlled for the effect of BMI as a covariate in regression analyses to mitigate the effect of obesity on FCD outcomes between patients with OSA and HCs. Hence, we concluded that the difference in FCD in this study was caused by OSA.

Differences in FCD Between Patients with OSA and HCs

Our study identified reduced short-range FCD in the right PoCG among patients with OSA, and we observed a negative correlation between short-range FCD values in the PoCG and delayed recall scores on the MoCA. The PoCG is an important component of the SMN, which is crucial for sensory and perceptual integration.[35] SMN dysfunction is associated with sleep disorders and OSA severity,[36] potentially resulting in reduced information-processing speed and cognitive dysfunction. Previous studies have documented structural and functional deficits in the PoCG, including decreased ReHo,[7] fractional anisotropy,[37] FC[38] and reduced cerebral blood flow (CBF).[39] These deficits may stem from altered sensory inputs, and motor outputs in the upper airway, resulting in decreased lingual muscle tissue tone and airway collapse.[40] A study showed that children with OSA exhibited a significant reduction in lymph node mediated

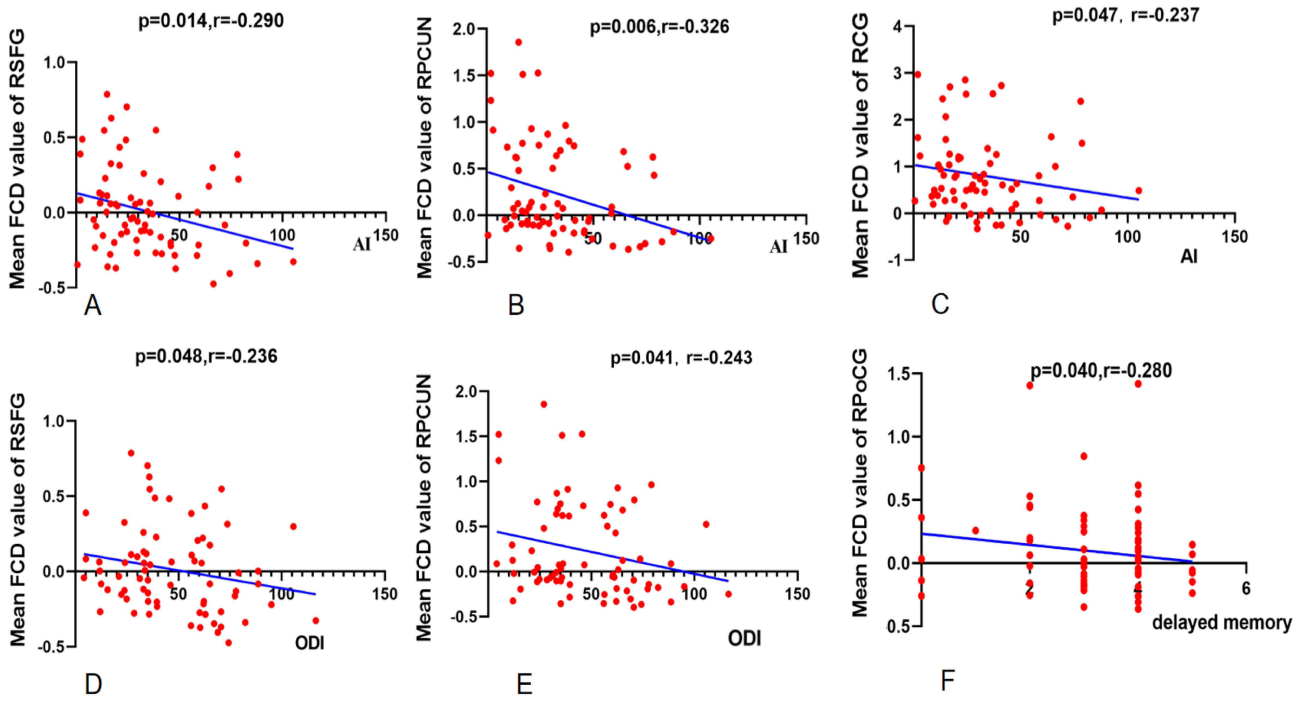

Figure 6 In OSA patients, there was a significant correlation between mean FCD values with intergroup differences (OSA patients vs HCs) and clinical assessments. (**A**) there was a significant correlation between mean FCD values in the right superior frontal gyrus and AI (p=0.014, r=−0.290). (**B**) there was a significant correlation between mean FCD values and AI in the right precuneus (p=0.006, r=−0.326). (**C**) there was a significant correlation between mean FCD values in the right cingulate gyrus and AI (p=0.047, r=−0.237). (**D**) there was a significant correlation between mean FCD values in the right superior frontal gyrus and ODI (p=0.048, r=−0.236). (**E**) there was a significant correlation between mean FCD values and ODI in the right precuneus (p=0.041, r=−0.243). (**F**) there was a significant correlation between mean FCD values in the right postcentral gyrus and delayed recall (p=0.040, r=−0.280).

Abbreviations: FCD, function connectivity density; AI, arousal index; ODI, oxygen desaturation index. SFG, Superior Frontal Gyrus; PCUN, Precuneus; CG, Cingulate Gyrus; PoCG, Postcentral Gyrus.

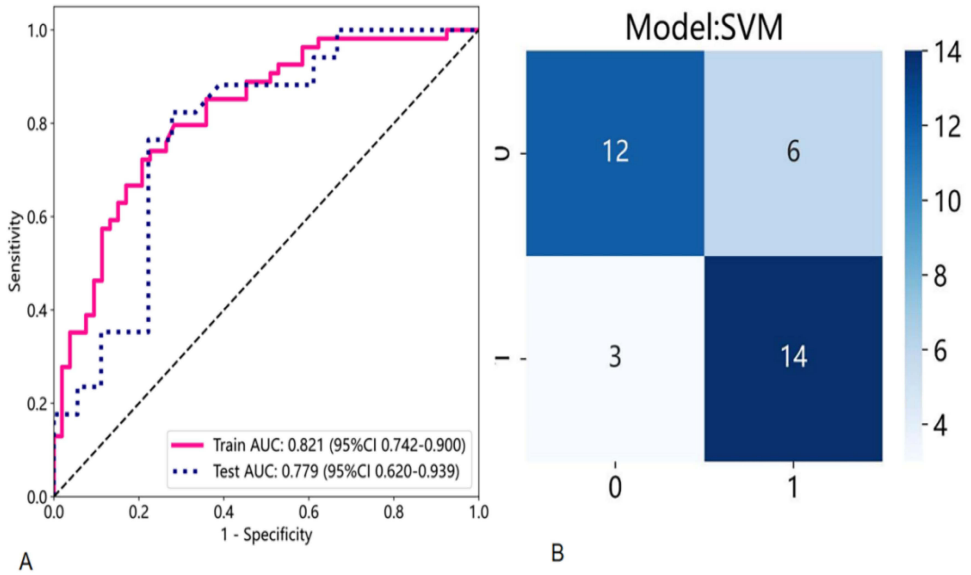

Figure 7 Construction of SVM classification model and confusion matrix using FCD values of differential brain regions as features. (**A**) ROC curve analysis of mean FCD values for all differential brain areas. The Train AUC was 82.1%, Test AUC was 77.9%; (**B**) The confusion matrix indicates that the test set accuracy 74.3%;sensitivity 82.4%; specificity 66.7%; AUC77.9%; $p < 0.001$.

Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; FCD, function connectivity density; SVM, support vector machine.

centrality in regions such as the PoCG.[41] Our findings were in partial agreement with these findings. Moreover, studies have proposed that brain regions within or near sensory and motor areas typically exhibit high local connectivity. Regions with preferential short-range connectivity are characterized by low energy costs and high clustering coefficients.[42] We hypothesize that OSA would increase energy costs by affecting the low-energy-cost components of the SMN,[5,43] such as hubs with preferential short-range connectivity, which may be selectively attacked, leading to reduced short-range FCD in the right PoCG. This phenomenon was associated with a reduced ability to integrate the network and cognitive dysfunction in patients with OSA.

The presence of both a decrease in short-range FCD, and an increase in long-range FCD, in the right CG signifies significant dysfunction and alteration in this region. The right CG,[44] located on the medial surface of the cerebral hemispheres, is a key component of the DMN. It plays a key role in respiration, mood control, and cognitive functioning. Eun et al[45,46] found that the underlying cause of respiratory and mood disturbances in OSA may be related to reduced concentrations of gray matter in the CG. Previous studies have demonstrated FC disruptions[14] within the hippocampus in patients with OSA, affecting the posterior cingulate cortex. Studies have also shown that dynamic ReHo values[47] and CG degree centrality values[48] are reduced in patients with OSA, partially aligning with our findings. Our study also showed a reduction in long-range FCD in the right PCUN compared to the normal group. Tomasi and Wavelow noted that the PCUN has significant long-range FCD in healthy individuals[49], suggesting its importance as a hub for remote connectivity with other brain regions. The PCUN, a unique hub in the DMN, plays a critical role in supporting complex cognition and behavior.[50] Sleep fragmentation and intermittent hypoxia in patients with OSA can trigger elevated oxidative stress and subsequent inflammation, potentially leading to vasogenic edema in brain structures.[51] This may contribute significantly to dysfunction of the posterior CG and PCUN, further contributing to diminished FCD values. However, the exact mechanism underlying the increase in FCD remains unclear, and the increase in FCD in patients with OSA may be a compensatory process for the decrease in FCD in other brain regions to maintain normal brain function. In summary, the disrupted balance between long- and short-range FCD in the right CG and right PCUN may indicate FC reorganization within the DMN, warranting further investigation.

In our study, patients with OSA exhibited reduced long-range FCD in the right SFG and left MFG, along with decreased short-range FCD in the left SFG and right MFG compared to HCs. These finding indicate that reduced FCD is more likely in the anterior brain regions, suggesting deficits in neural connectivity within these regions. Reduced FCs implies impaired information processing exchange, and reductions in long-range FCD may hinder the diversity of inputs and outputs within brain regions. Different parts of the SFG and MFG are involved in the FPCN[52] and play a role in modulating perceptual attention.[53] Past studies[38,54] have shown that global network connectivity in the prefrontal regions is significantly reduced in patients with OSA. The SFG[55] is crucial for the resting state, and cognitive control tasks, among others. A previous study observed structural alterations, including volume atrophy and cortical thinning,[56] in this region among patients with OSA, potentially contributing to changes in long- and short-range FCD. Similarly, the MFG,[57] a highly interconnected cortical structure, is involved in a diversity of tasks, such as attention processing and comprehension tasks. Studies[7] have indicated decreased ReHo in the left MFG, contrary to the findings in HCs, implying that nocturnal intermittent hypoxemia may impair FPCN function, resulting in cognitive dysfunction. Moreover, frontal lobe dysfunction is proposed as a potential key neuropathophysiological mechanism underlying neurocognitive impairment in patients with moderate to severe OSA. Research[58,59] has shown significant decrease in resting state FC in the prefrontal, parietal, and temporal lobes. Li et al[34] found that 3 months of CPAP treatment increased the connectivity of the frontal lobe. These findings provide unique insights into the system-level circuitry underlying cognitive control. However, our study found no correlation between changes in spontaneous activity in the SFG and MFG and cognitive scale scores. Collectively, our findings suggest that the prefrontal lobes are compromised, with reduced FCD indicating disrupted resting-state functional activity and impaired communication ability within these regions. These alterations may also be related to neurodegenerative processes in patients with OSA.

Potential Clinical Value of SVM Analysis

In recent years, more and more scholars have combined machine learning techniques with diagnostic prediction models for various diseases,[22,23,54] and enhanced sensitivity and accuracy compared to traditional methods. Our results showed that FCD values in different brain regions were able to effectively distinguish patients with OSA and HCs with high

accuracy, sensitivity and specificity and efficacy of up to 82.1%. Long et al[60] classified OSA and HC with the altered thalamic dFC variability, with a classification accuracy of 77.8%. This suggests that FCD in differential brain regions is somehow more effective in identifying OSA patients and HCs, can serve as potential imaging biomarkers, and is also expected to promote and accelerate the clinical value of OSA diagnosis and treatment through the SVM classifier.[61]

Limitations

Our study had three limitations. First, patients with OSA tend to seek treatment after the development of a moderate to severe phenotype and the higher prevalence in men may limit the generalizability of our findings. Future studies should include more female participants and patients with mild OSA. Second, the sample size used in this paper is not large enough, which has some effect on the SVM classification accuracy. Third, we only explored changes in resting-state FCD in patients with OSA. Subsequent studies should explore differences in whole-brain dynamic FCD among patients with OSA, potentially integrating molecular-level investigations with genetic indicators.

Conclusion

In conclusion, we used the FCD mapping method to characterize the effects of brain activity in OSA patients. The differential brain regions in OSA patients mainly involved three networks, DMN, SMN and FPCN, and the differential brain region FCD values correlated with the delayed recall subregion of the Cognitive Scale and with some clinical indicators. In addition, through SVM modeling, we found that the FCD values of the differential brain regions can be effectively distinguished between OSA patients and HCs, as characterized by the FCD values of the differential brain regions. This suggests that an objective characterization of the distribution of brain FCD patterns contributes to a better understanding of the unique patterns of cognitive dysfunction caused by OSA and its underlying compensatory mechanisms.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

The authors declare no potential conflicts of interest in this work.

References

1. Błaszczyk B, Martynowicz H, Więckiewicz M. et al. Prevalence of headaches and their relationship with obstructive sleep apnea (OSA) - Systematic review and meta-analysis. *Sleep Med Rev*. 2024;73:101889. doi:10.1016/j.smrv.2023.101889
2. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687–698. doi:10.1016/S2213-2600(19)30198-5
3. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev*. 2017;34:70–81. doi:10.1016/j.smrv.2016.07.002
4. Marchi NA, Solelhac G, Berger M, et al. Obstructive sleep apnoea and 5-year cognitive decline in the elderly. *Eur Respir J*. 2023;61(4):2201621. doi:10.1183/13993003.01621-2022

5. Huang L, Shu Y, Liu X, et al. Abnormal dynamic functional connectivity in the hippocampal subregions of patients with untreated moderate-to-severe obstructive sleep apnea. *Sleep Med*. 2023;112:273–281. doi:10.1016/j.sleep.2023.10.037
6. Song X, Roy B, Vacas S, et al. Brain regional homogeneity changes after short-term positive airway pressure treatment in patients with obstructive sleep apnea. *Sleep Med*. 2022;91:12–20. doi:10.1016/j.sleep.2022.02.005
7. Zhou L, Shan X, Peng Y, et al. Reduced regional homogeneity and neurocognitive impairment in patients with moderate-to-severe obstructive sleep apnea. *Sleep Med*. 2020;75:418–427. doi:10.1016/j.sleep.2020.09.009
8. Xie W, Shu Y, Liu X, et al. Abnormal Spontaneous Brain Activity and Cognitive Impairment in Obstructive Sleep Apnea. *Nat Sci Sleep*. 2022;14:1575–1587. doi:10.2147/NSS.S376638
9. Zeng Y, Shu Y, Liu X, et al. Frequency-specific alterations in intrinsic low-frequency oscillations in newly diagnosed male patients with obstructive sleep apnea. *Front Neurosci*. 2022;16(987015). doi:10.3389/fnins.2022.987015
10. Torelli F, Moscufo N, Garreffa G, et al. Cognitive profile and brain morphological changes in obstructive sleep apnea. *Neuroimage*. 2011;54 (2):787–793. doi:10.1016/j.neuroimage.2010.09.065
11. Kong L, Li H, Shu Y, et al. Aberrant Resting-State Functional Brain Connectivity of Insular Subregions in Obstructive Sleep Apnea. *Front Neurosci*. 2021;15:765775. doi:10.3389/fnins.2021.765775
12. Park HR, Cha J, Joo EY, et al. Altered cerebrocerebellar functional connectivity in patients with obstructive sleep apnea and its association with cognitive function. *Sleep*. 2022;45(1):zsab209. doi:10.1093/sleep/zsab209
13. Byun J-I, Jahng G-H, Ryu C-W, et al. Altered functional connectivity of the ascending reticular activating system in obstructive sleep apnea. *Sci Rep*. 2023;13(1):8731. doi:10.1038/s41598-023-35535-4
14. Song X, Roy B, Kang DW, et al. Altered resting-state hippocampal and caudate functional networks in patients with obstructive sleep apnea. *Brain Behav*. 2018;8(6):e00994. doi:10.1002/brb3.994
15. Liu X, Chen L, Duan W, et al. Abnormal Functional Connectivity of Hippocampal Subdivisions in Obstructive Sleep Apnea: a Resting-State Functional Magnetic Resonance Imaging Study. *Front Neurosci*. 2022;16:850940. doi:10.3389/fnins.2022.850940
16. Tomasi D, Volkow ND. Association between functional connectivity hubs and brain networks. *Cereb Cortex*. 2011;21(9):2003–2013. doi:10.1093/cercor/bhq268
17. Tomasi D, Volkow ND. Functional connectivity density mapping. *Proc Natl Acad Sci U S A*. 2010;107(21):9885–9890. doi:10.1073/pnas.1001414107
18. Lopez-Vilaret KM, Fernandez-Alvarez M, Shokri-Kojori E, et al. Pre-diabetes is associated with altered functional connectivity density in cortical regions of the default-mode network. *Front Aging Neurosci*. 2022;14(1034355). doi:10.3389/fnagi.2022.1034355
19. Dai L, Yu Y, Zhao H, et al. Altered local and distant functional connectivity density in chronic migraine: a resting-state functional MRI study. *Neuroradiology*. 2021;63(4):555–562. doi:10.1007/s00234-020-02582-x
20. Mao Y, Liao Z, Liu X, et al. Disrupted balance of long and short-range functional connectivity density in Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients: a resting-state fMRI study. *Ann Transl Med*. 2021;9(1):65. doi:10.21037/atm-20-7019
21. Tang L, Tian Y, Wang X, et al. A simple and reliable instance selection for fast training support vector machine: valid Border Recognition. *Neural Netwk*. 2023;166:379–395. doi:10.1016/j.neunet.2023.07.018
22. Bu S, Pang H, Li X, et al. Structural and Functional Alterations of Motor-Thalamus in Different Motor Subtype of Parkinson's Disease: an Individual Study. *Acad Radiol*. 2023;S1076-6332(23):00520. doi:10.1016/j.acra.2023.09.041
23. Zheng W, Liu H, Li Z, et al. Classification of Alzheimer's disease based on hippocampal multivariate morphometry statistics. *CNS Neurosci Ther*. 2023;29(9):2457–2468. doi:10.1111/cns.14189
24. Jafari B, Mohsenin V. Polysomnography, Clinics in Chest Medicine. *Clinics in Chest Medicine*. 2010;31(2):287–297. doi:10.1016/j.ccm.2010.02.005
25. Berry RB, Brooks R, Gamaldo C, et al. AASM Scoring Manual Updates for 2017 (Version 2.4). *J Clin Sleep Med*. 2017;13(5):665–666. doi:10.5664/jcsm.6576
26. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x
27. Johns MW. A New Method for Measuring Daytime *Sleep*iness: the Epworth *Sleep*iness Scale. *Sleep*. 1991;14(6):540–545. doi:10.1093/sleep/14.6.540
28. He Y, Chen ZJ, Evans AC. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex*. 2007;17 (10):2407–2419. doi:10.1093/cercor/bhl149
29. Zhang D, Liu S, Huang Y, et al. Altered Functional Connectivity Density in Type 2 Diabetes Mellitus with and without Mild Cognitive Impairment. *Brain Sci*. 2023;13(1):144. doi:10.3390/brainsci13010144
30. Tomasi D, Shokri-Kojori E, Volkow ND. High-Resolution Functional Connectivity Density: hub Locations, Sensitivity, Specificity, Reproducibility, and Reliability. *Cereb Cortex*. 2016;26(7):3249–3259. doi:10.1093/cercor/bhv171
31. Leung K, Zhang B, Tan J, et al. Prediction of Total Knee Replacement and Diagnosis of Osteoarthritis by Using Deep Learning on Knee Radiographs: data from the Osteoarthritis Initiative. *Radiology*. 2020;296(3):584–593. doi:10.1148/radiol.2020192091
32. Yh K, Sw K, Wr R, et al. Portable evaluation of obstructive sleep apnea in adults: a systematic review. *Sleep Med Rev*. 2023;68:101743. doi:10.1016/j.smrv.2022.101743
33. Drager LF, Togeiro SM, Polotsky VY, et al. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. *J Am Coll Cardiol*. 2013;62(7):569–576. doi:10.1016/j.jacc.2013.05.045
34. Li H, Li L, Kong L, et al. Frequency-Specific Regional Homogeneity Alterations and Cognitive Function in Obstructive Sleep Apnea Before and After Short-Term Continuous Positive Airway Pressure Treatment. *Nat Sci Sleep*. 2021;13:2221–2238. doi:10.2147/NSS.S344842
35. Hong K-S, Khan MNA, Ghafoor U. Non-invasive transcranial electrical brain stimulation guided by functional near-infrared spectroscopy for targeted neuromodulation: a review. *J Neural Eng*. 2022;19(4):041001. doi:10.1088/1741-2552/ac857d
36. Zeng L, Shu Y, Xie W, et al. Functional Connectivity Changes in Amygdala Subregions of Obstructive Sleep Apnea Patients After Six Months of Continuous Positive Airway Pressure Treatment. *NSS*. 2024;16:99–109. doi:10.2147/NSS.S442253
37. Lee M-H, Yun C-H, Min A, et al. Altered structural brain network resulting from white matter injury in obstructive sleep apnea. *Sleep*. 2019;42(9): zsz120. doi:10.1093/sleep/zsz120
38. Park B, Palomares JA, Woo MA, et al. Disrupted functional brain network organization in patients with obstructive sleep apnea. *Brain Behav*. 2016;6(3):e00441. doi:10.1002/brb3.441

39. Baril -A-A, Gagnon K, Arbour C, et al. Regional Cerebral Blood Flow during Wakeful Rest in Older Subjects with Mild to Severe Obstructive *Sleep* Apnea. *Sleep*. 2015;38(9):1439–1449. doi:10.5665/sleep.4986
40. Ruehland WR, Rochford PD, Pierce RJ, et al. Genioglossus muscle responses to resistive loads in severe OSA patients and healthy control subjects. *J Appl Physiol*. 2019;127(6):1586–1598. doi:10.1152/japplphysiol.00186.2019
41. Li Y, Wen H, Li W, et al. Diffusion kurtosis imaging tractography reveals disrupted white matter structural networks in children with obstructive sleep apnea syndrome. *Brain Imaging Behav*. 2023;18(1):92–105. doi:10.1007/s11682-023-00809-y
42. Sepulcre J, Liu H, Talukdar T, et al. The organization of local and distant functional connectivity in the human brain. *PLoS Comput Biol*. 2010;6(6): e1000808. doi:10.1371/journal.pcbi.1000808
43. Santarnecchi E, Sicilia I, Richiardi J, et al. Altered cortical and subcortical local coherence in obstructive sleep apnea: a functional magnetic resonance imaging study. *J Sleep Res*. 2013;22(3):337–347. doi:10.1111/jsr.12006
44. Zhang D, Huang Y, Liu S, et al. Structural and functional connectivity alteration patterns of the cingulate gyrus in Type 2 diabetes. *Ann Clin Transl Neurol*. 2023;10(12):2305–2315. doi:10.1002/acn3.51918
45. Joo EY, Tae WS, Lee MJ, et al. Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. *Sleep*. 2010;33 (2):235–241. doi:10.1093/sleep/33.2.235
46. Huang L, Li H, Shu Y, et al. Changes in Functional Connectivity of Hippocampal Subregions in Patients with Obstructive Sleep Apnea after Six Months of Continuous Positive Airway Pressure Treatment. *Brain Sci*. 2023;13(5):838. doi:10.3390/brainsci13050838
47. Li K, Shu Y, Liu X, et al. Dynamic regional homogeneity alterations and cognitive impairment in patients with moderate and severe obstructive sleep apnea. *Front Neurosci*. 2022;16:940721. doi:10.3389/fnins.2022.940721
48. Li H, Li L, Shao Y, et al. Abnormal Intrinsic Functional Hubs in Severe Male Obstructive Sleep Apnea: evidence from a Voxel-Wise Degree Centrality Analysis. *PLoS One*. 2016;11(10):e0164031. doi:10.1371/journal.pone.0164031
49. Cohen AD, Tomasi D, Shokri-Kojori E, et al. Functional connectivity density mapping: comparing multiband and conventional EPI protocols. *Brain Imaging Behav*. 2018;12(3):848–859. doi:10.1007/s11682-017-9742-7
50. Utevsky AV, Smith DV, Huettel SA. Precuneus Is a Functional Core of the Default-Mode Network. *J Neurosci*. 2014;34(3):932–940. doi:10.1523/ JNEUROSCI.4227-13.2014
51. Lin W-C, Huang -C-C, Chen H-L, et al. Longitudinal brain structural alterations and systemic inflammation in obstructive sleep apnea before and after surgical treatment. *J Transl Med*. 2016;14(1):139. doi:10.1186/s12967-016-0887-8
52. Yang W, Zhuang K, Liu P, et al. Memory Suppression Ability can be Robustly Predicted by the Internetwork Communication of Frontoparietal Control Network. *Cereb Cortex*. 2021;31(7):3451–3461. doi:10.1093/cercor/bhab024
53. Dixon ML, De La Vega A, Mills C, et al. Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. *Proc Natl Acad Sci U S A*. 2018;115(7):E1598–E1607. doi:10.1073/pnas.1715766115
54. He D, Ren D, Guo Z, et al. Insomnia disorder diagnosed by resting-state fMRI-based SVM classifier. *Sleep Med*. 2022;95:126–129. doi:10.1016/j. sleep.2022.04.024
55. Briggs RG, Khan AB, Chakraborty AR, et al. Anatomy and White Matter Connections of the Superior Frontal Gyrus. *Clin Anat*. 2020;33 (6):823–832. doi:10.1002/ca.23523
56. Zhang M, Gao X, Yang Z, et al. Shared gray matter alterations in subtypes of addiction: a voxel-wise meta-analysis. *Psychopharmacology*. 2021;238(9):2365–2379. doi:10.1007/s00213-021-05920-w
57. Briggs RG, Lin Y-H, Dadario NB, et al. Anatomy and White Matter Connections of the Middle Frontal Gyrus. *World Neurosurg*. 2021;150:e520–e529. doi:10.1016/j.wneu.2021.03.045
58. Chen L, Fan X, Li H, et al. Topological Reorganization of the Default Mode Network in Severe Male Obstructive Sleep Apnea. *Front Neurol*. 2018;9(363). doi:10.3389/fneur.2018.00363
59. Martinez Villar G, Daneault V, Martineau-Dussault M-È, et al. Altered resting-state functional connectivity patterns in late middle-aged and older adults with obstructive sleep apnea. *Front Neurol*. 2023;14(1215882). doi:10.3389/fneur.2023.1215882
60. Long T, Shu Y, Liu X, et al. Abnormal temporal variability of thalamo-cortical circuit in patients with moderate-to-severe obstructive sleep apnea. *J Sleep Res*. 2024;33(5):e14159. doi:10.1111/jsr.14159
61. Mourão-Miranda J, Bokde ALW, Born C, et al. Classifying brain states and determining the discriminating activation patterns: support Vector Machine on functional MRI data. *NeuroImage*. 2005;28(4):980–995. doi:10.1016/j.neuroimage.2005.06.070