

Aberrant spontaneous low-frequency brain activity in male patients with severe obstructive sleep apnea revealed by resting-state functional MRI

Hai-Jun Li^{1,*}

Xi-Jian Dai^{1,2,*}

Hong-Han Gong¹

Xiao Nie¹

Wei Zhang³

De-Chang Peng¹

¹Department of Radiology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, People's Republic of China; ²Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong Special Administrative Region, People's Republic of China; ³Department of Pneumology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, People's Republic of China

*These authors contributed equally to this work

Background: The majority of previous neuroimaging studies have demonstrated both structural and functional abnormalities in obstructive sleep apnea (OSA). However, few studies have focused on the regional intensity of spontaneous fluctuations during the resting state and the relationship between the abnormal properties and the behavioral performances. In the present study, we employed the amplitude of low-frequency fluctuation (ALFF) method to explore the local features of spontaneous brain activity in OSA patients (OSAs).

Methods: Twenty-five untreated male severe OSAs and 25 age-matched and years-of-education-matched male good sleepers (GSs) were included in this study. The ALFF method was used to assess the local features of spontaneous brain activity. The mean signal values of the altered ALFF areas were analyzed with receiver operating characteristic curve. Partial correlation analysis was used to explore the relationship between the observed mean ALFF values of the different areas and the behavioral performances.

Results: Compared with GSs, OSAs had significantly higher scores for body mass index, apnea-hypopnea index, arterial oxygen saturation <90%, arousal index, and Epworth Sleepiness Scale (ESS) score; furthermore, OSAs had significantly lower scores for rapid eye movement sleep and in the Montreal Cognitive Assessment (MoCA). Compared with GSs, OSAs showed significant lower-ALFF areas in the cluster of the right precuneus and bilateral posterior cingulate gyrus, as well as a higher-ALFF area in the left inferior frontal gyrus. The area under the curve values of the lower- and higher-ALFF areas were 0.90 and 0.93, respectively. Further diagnostic analysis exhibited that the sensibility and specificity of the two clusters were 80% and 92%, respectively. The mean signal value of the lower-ALFF cluster displayed significant positive correlations with lowest oxygen saturation ($r=0.447$, $P=0.025$) and MoCA score ($r=0.405$, $P=0.045$).

Conclusion: OSAs may involve in a dysfunction in the default mode network and an adaptive compensatory response in the frontal lobe, which reflect the underlying pathophysiology of cognitive impairment.

Keywords: obstructive sleep apnea, amplitude of low-frequency fluctuation, functional magnetic resonance imaging, resting state, spontaneous activity, blood oxygen-level-dependent

Introduction

Obstructive sleep apnea (OSA), characterized by repeated obstructions of upper airway with intermittent hypoxic exposure, is associated with multiple detrimental physiological and psychological consequences, in addition to being associated with cardiorespiratory diseases, including pulmonary hypertension,¹ systemic hypertension,² cardiac arrhythmias,³ cardiac ischemia⁴ and cerebral ischemia.⁵ OSA may also cause daytime sleepiness,⁶ increase the risk of a traffic accident,⁷ and diminish both quality of life⁸ and work performance,⁹ as well as being accompanied by impairment in

Correspondence: De-Chang Peng
Department of Radiology, The First Affiliated Hospital of Nanchang University, 17 Yongwai Zheng Street, Donghu District, Nanchang City 330006, Jiangxi, People's Republic of China
Tel +86 791 8869 4457
Email pengdcdoctor@163.com

several cognitive domains, including attention and vigilance decrements, memory gaps, psychomotor dysfunction, and abnormalities in executive functions.^{10–12} On the basis of available population-based studies, OSA affects 3%–7% of adult men, 2%–5% of adult women,^{13–15} and up to 4% of children.^{16,17} The main pathophysiologic mechanism of cognitive deficits from OSA, including intermittent hypoxia, intermittent hypercapnia, and sleep fragmentation,¹⁸ are still unclear.

Previous neuroimaging studies have investigated 1) diminutions in gray matter concentration in the left hippocampus, left rectus gyrus, bilateral superior frontal gyrus, left precentral gyrus, bilateral frontomarginal gyrus, bilateral anterior cingulate gyrus, right insular gyrus, bilateral caudate nucleus, bilateral thalamus, bilateral amygdalo-hippocampus, bilateral inferior temporal gyrus, and cerebellum, and 2) gray matter volume deficits in bilateral hippocampus, bilateral lateral temporal areas, right cuneus, right middle temporal gyrus, left dorsolateral prefrontal cortex, right middle temporal gyrus, and left cerebellum using voxel-based morphometry techniques in OSA patients (OSAs).^{19–23} Moreover, diffusion tensor imaging studies showed a wide range of changes in white matter integrity within the corpus callosum, frontal cortex, temporal cortex, parietal cortexes, cingulate bundle, and cerebellum.^{24–26} A single-photon emission computed tomography study found that severe OSAs showed reduced cerebral blood flow in bilateral parahippocampal gyrus, right lingual gyrus, pericentral gyrus, and cuneus.²⁷ Decreased neural activations associated with cognitive impairment have been found in multiple brain regions, including the cingulate gyrus, dorsolateral prefrontal gyrus, inferior frontal gyrus, left postcentral gyrus, inferior and posterior parietal lobes, insula, and right putamen using task-state functional magnetic resonance imaging (fMRI) in OSAs.^{28–30} Recently, use of resting-state fMRI (rs-fMRI) has been increasing to investigate the ongoing neuronal processes in OSA. Although the majority of previous neuroimaging studies have focused on the brain structural and task-state functional changes of OSAs, few studies have evaluated the changes in blood oxygen-level-dependent (BOLD) signals of regional spontaneous activity of OSAs during resting state and their relationships with behavioral performances.

Amplitude of low-frequency fluctuation (ALFF), a newly developed rs-fMRI approach, calculates the square root of the power spectrum in a low-frequency range (0.01–0.08 Hz), for detecting the regional intensity of spontaneous fluctuations in BOLD signals.^{31–33} Furthermore, the ALFF has been proven

to have test–retest reliability³⁴ and has already been applied to patient studies investigating attention deficit hyperactivity disorder,³¹ sleep deprivation,³⁵ schizophrenia,³⁶ and early Alzheimer's disease.³⁷ However, it has not yet been used to explore the pathophysiological changes in OSAs. This study is the first to utilize ALFF as an index to investigate the intrinsic brain activity traits of OSAs and its potential mechanisms.

Materials and methods

Subjects

Twenty-five untreated male severe OSAs and 25 age-matched and years-of-education-matched male good sleepers (GSs) were included in this study from the Sleep Monitoring Room of the Respiratory Department of The First Affiliated Hospital of Nanchang University. Each subject was assessed by a detailed clinical interview and physical examination; in addition, the subjects completed a sleep questionnaire and underwent overnight polysomnography. The inclusion and exclusion criteria for the OSAs and GSs were as the same as in our previous study.^{38,39} The inclusion criteria for the OSAs were as follows: male sex; age >22 years but <60 years; and an apnea–hypopnea index (AHI) >30 events per hour. The exclusion criteria for both OSAs and GSs were as follows: 1) other sleep disorders, such as insomnia and sleep-related eating disorders; 2) history of cardiovascular disease, hypertension, or diabetes mellitus; 3) central nervous system disorders (neurodegenerative diseases, epilepsy, head injury, psychosis, hypothyroidism, or current depression); 4) left-handedness; 5) alcohol or illicit drug abuse; 6) current intake of psychoactive medications; and 7) contraindications to MRI, such as claustrophobia, metallic implants, or devices in the body. This study was approved by The Human Research Ethics Committee at The First Affiliated Hospital of Nanchang University, and all participants provided written informed consent forms.

Polysomnography

The day before the sleep studies, all OSAs and GSs were asked to refrain from drinking alcohol or caffeinated beverages. Full nocturnal polysomnography monitoring was performed on OSAs and GSs using the Respiromics LE-series physiological monitoring system (Alice 5 LE; Respiromics, Orlando, FL, USA) in the Sleep Center of our hospital. Standard electroencephalogram, electrooculogram, chin electromyogram, electrocardiogram, thoracic and abdominal movements, and snoring were recorded. Arterial oxygen saturation (SaO₂) was measured transcutaneously by fingertip

pulse oximetry. In accordance with the American Academy of Sleep Medicine guidelines, apnea was defined as the continuous cessation of airflow for more than 10 seconds and hypopnea was defined as a decrease in airflow by $>30\%$ with arousal or oxygen desaturation $>4\%$.^{40,41} The AHI was calculated as the average of the total number of apnea and hypopnea events experienced per hour of sleep. Subjects' performances were recorded on videotape and were continuously observed by a polysomnography technician. Polysomnography was performed from 10 pm to 6 am next morning.

Neuropsychological evaluation

All subjects filled in a sleep questionnaire to assess their daytime sleepiness by the Epworth Sleepiness Scale (ESS), with scores between 0 and 24.⁴² A score higher than 6 was considered somnolence. All subjects underwent a cognitive assessment using the Montreal Cognitive Assessment (MoCA)⁴³ tool, administered by two independent neuropsychologists, to evaluate their executive function, naming, attention, calculation, language, abstraction, memory, and orientation. The total MoCA score is 30. A total MoCA score <26 indicates cognitive impairment, whereas a score ≥ 26 indicates normal cognitive function. If the length of schooling was <12 years, one point was added to the total score, so as to adjust for educational bias.⁴⁴

MRI parameters

MRI scanning was performed on a 3-Tesla MRI scanner (Siemens, Erlangen, Germany). High-resolution T1-weighted images were acquired with a three-dimensional spoiled gradient-recalled echo sequence in a sagittal orientation: 176 images (repetition time = 1,900 ms; echo time = 2.26 ms; thickness = 1.0 mm; gap = 0.5 mm; acquisition matrix = 256×256 ; field of view = 250×250 mm², flip angle = 9°) were obtained. Finally, 240 functional images (repetition time = 2,000 ms; echo time = 30 ms; thickness = 4.0 mm; gap = 1.2 mm; acquisition matrix = 64×64 ; flip angle = 90° ; field of view = 230×230 mm²; 30 axial slices with gradient-recalled echo-planar imaging [EPI] pulse sequence) covering the whole brain were obtained.

fMRI data analysis

Functional data were checked using MRIcro software (www.MRIcro.com) to exclude defective data. The first ten time points of the functional images were discarded due to the possible instability of the initial MRI signals and the participants' adaptation time to the scanning environment.

On the basis of MATLAB2010a (Mathworks, Natick, MA, USA), the remainder of the data preprocessing was performed by DPARSFA (<http://rfmri.org/DPARSF>) software, including DICOM form transformation, slice timing, head motion correction, spatial normalization, smoothing with a Gaussian kernel of $6 \times 6 \times 6$ mm³ full width at half maximum (FWHM). Motion time courses were obtained by estimating the values for translation (mm) and rotation (degrees) for each subject. Participants who had >1.5 mm maximum displacement in *x*, *y*, or *z* planes and 1.5° of angular motion during the whole fMRI scans were rejected. The Friston six head motion parameters were used to regress out head motion effects based on recent work showing that higher-order models were more effective in removing head motion effects.^{45,46} Linear regression was also applied to remove other sources of spurious covariates along with their temporal derivatives, including the signal from a ventricular region of interest (ROI) and the signal from a region centered in the white matter.⁴⁷ Of note, the global signal was not regressed out in the present data, as in the study by Guo et al⁴⁸ for the reason that there is still a controversy around the removal of the global signal in the preprocessing step of resting-state data.^{47,49} After head-motion correction, the fMRI images were spatially normalized to the Montreal Neurological Institute (MNI) space using the standard EPI template and resampling the images at a resolution of $3 \times 3 \times 3$ mm³. After preprocessing, the time series for each voxel were linearly detrended to reduce low-frequency drift, physiological high-frequency respiratory and cardiac noise, and time series linear detrending. The time series for each voxel were transformed to the frequency domain, and the power spectrum was then obtained. Because the power of a given frequency is proportional to the square of the amplitude of this frequency component, the square root was calculated at each frequency of the power spectrum, and the averaged square root was obtained across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. The details of ALFF calculation are as described in a previous study.³¹ To reduce the global effects of variability across the participants, the ALFF of each voxel was divided by the global mean ALFF value for each participant.

Statistical analysis

Subject characteristics, including age, body mass index (BMI), education, ESS score, MoCA score, and sleep-disordered breathing parameters, were tested using independent sample *t*-tests to compare OSAs with GSs using IBM Statistical Package for the Social Sciences version 19.0 (SPSS 19.0), and a *P*-value <0.05 was deemed significant. For functional data,

two-sample Student's *t*-test was used to analyze the difference between the two groups, with age and years of education as nuisance covariates of no interest. A corrected significance level of individual voxel $P < 0.001$ and a cluster volume (V) $\geq 270 \text{ mm}^3$ (a minimum continuous V of 270 mm^3), using a false discovery rate (FDR)-corrected cluster threshold of $P < 0.05$, was used to determine statistical significance.

On the basis of the ALFF findings, the brain regions that demonstrated significant level of difference between groups were indentified. These regions were classified as ROIs and saved as masks using the REST Version1.8 software ([http://www.resting-fmri.Sourceforge.net](http://www.resting-fmri.sourceforge.net)). For each ROI, the mean ALFF value was extracted by averaging the ALFF values over all voxels for each OSA. Finally, the mean ALFF values were entered into IBM SPSS 19.0 to calculate their correlations with the behavioral performances.

Results

Demographic and clinical results

Demographic and clinical characteristics of each group are summarized in Table 1. The OSAs had significantly higher scores for BMI ($t = 6.25$, $P < 0.001$), AHI ($t = 15.51$, $P < 0.001$), $\text{SaO}_2 < 90\%$ ($t = 6.66$, $P < 0.001$), arousal index ($t = 6.85$, $P < 0.001$), and ESS score ($t = 7.64$, $P < 0.001$) and had significantly lower scores for rapid eye movement (REM) sleep ($t = -5.4$, $P < 0.001$) and MoCA ($t = -2.16$, $P = 0.036$) than the GSs.

Table 1 Demographic and clinical characteristics of OSAs and GSs

Characteristic	OSAs (N=25)		GSs (N=25)		P*
	Mean	SD	Mean	SD	
Age, years	39.4	1.7	39.5	1.6	0.946
Education, years	11.9	3.1	10.8	3.8	0.258
BMI, kg/m ²	27.8	3.4	22.9	2.1	<0.001*
Total sleep time, minutes	373.6	31.8	397.4	24.9	0.005*
AHI, per hour	60.0	18.6	2.2	1.3	<0.001*
N ₁ , %	32.2	20.4	10.6	4.0	<0.001*
N ₂ , %	45.2	17.4	48.6	6.4	0.361
N ₃ , %	14.2	9.3	21.0	5.2	<0.001*
REM, %	8.4	8.6	20.4	6.9	<0.001*
$\text{SaO}_2 < 90\%$	26.5	19.7	0.2	0.2	<0.001*
Lowest SaO_2	64.0	12.3	90.63	5.72	<0.001*
Arousal index, per hour	44.0	23.3	11.8	3.0	<0.001*
ESS score	15.2	7.3	1.1	1.1	<0.001*
MoCA score	25.7	2.3	27.1	2.3	0.036*

Notes: $\text{SaO}_2 < 90\%$, percentage of total sleep time spent at oxygen saturations less than 90%; N₁, N₂, N₃, REM%, percentage of total sleep time at diagnostic polysomnography spent in relevant stages; Lowest SaO_2 , lowest oxygen saturations; MoCA, Montreal Cognitive Assessment; P*, independent samples *t*-tests; * $P < 0.05$.

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; N, number; OSAs, patients with severe obstructive sleep apnea; GSs, good sleepers; REM, rapid eye movement; SD, standard deviation.

ALFF results

Compared with GSs, OSAs showed significant lower-ALFF areas in the cluster of right precuneus and bilateral posterior cingulate gyrus and a higher-ALFF area in the left inferior frontal gyrus. The details are presented in Table 2 and Figure 1. The mean ALFF values of these altered areas were extracted (Figure 2).

Correlation results

In the OSAs, the AHI score displayed a significant positive correlation with the arousal index ($r = 0.642$, $P = 0.001$) and negative correlations with REM% ($r = -0.429$, $P = 0.032$) and MoCA score ($r = -0.405$, $P = 0.045$). N2% (percentage of total sleep time at diagnostic polysomnography spent in the relevant stage) displayed negative correlations with REM% ($r = -0.584$, $P = 0.002$) and ESS score ($r = -0.531$, $P = 0.006$). BMI displayed significant positive correlation with arousal index ($r = 0.582$, $P = 0.002$) and negative correlation with the lowest oxygen saturation ($r = -0.647$, $P < 0.001$).

The mean signal value of the observed lower-ALFF area displayed significant positive correlations with the lowest oxygen saturation ($r = 0.447$, $P = 0.025$) and MoCA score ($r = 0.405$, $P = 0.045$).

Receiver operating characteristic curve

Because different ALFF areas were found between OSAs and GSs, they might be utilized as markers to separate the OSAs from the GSs. To test this possibility, the mean ALFF values of the different brain regions were extracted and used for analysis of the receiver operating characteristic curves. In the present study, the values for the areas under the curves of the left inferior frontal gyrus and the cluster of right precuneus and bilateral posterior cingulate gyrus were 0.93 and 0.90, respectively. Further diagnostic analysis showed that the sensibility and specificity of the two clusters were 92% and 80%, respectively. The details are presented in Figure 3.

Discussion

Our previous study⁵⁰ had demonstrated that many brain areas have obvious sex differences after normal sleep status and during sleep loss status. In this study, so as to avoid the influence of the sex differences or a lopsided sex ratio, only male OSAs were recruited. Our study is the first to investigate the effect of OSA on resting-state brain activity using the ALFF method. In our current study, we found that OSAs showed higher ALFF in the left inferior frontal lobe and lower ALFF in the cluster of right precuneus and bilateral

Table 2 Two-sample *t*-test differences between OSAs and GSs using ALFF method

Conditions	Brain regions	V (mm ³)	t-score of peak voxel	MNI coordinates of peak voxel			P
OSAs < GSs	Right precuneus/posterior cingulate gyrus	1,350	-5.44	0	-51	30	<0.001*
OSAs > GSs	Left inferior frontal gyrus	297	5.37	-27	39	-21	<0.001*

Notes: The between-condition statistical threshold was set at cluster size with $P < 0.05$, voxel with $P < 0.001$, and $V \geq 270$ mm³, corrected by FDR. *P**, independent samples *t*-tests; * $P < 0.05$.

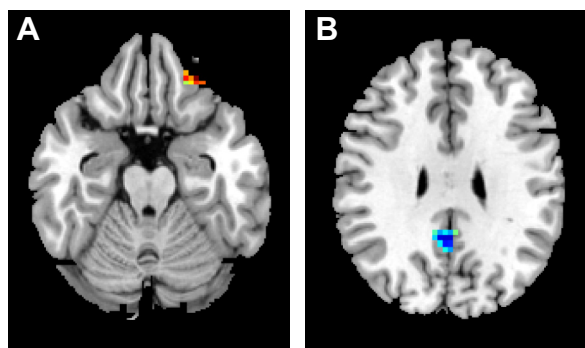
Abbreviations: ALFF, amplitude of low-frequency fluctuation; FDR, false discovery rate; GSs, good sleepers; MNI, Montreal Neurological Institute; OSAs, patients with severe obstructive sleep apnea; V, volume.

posterior cingulate gyrus, compared with GSs, and showed lower MoCA score than GSs. Moreover, the observed lower-ALFF area displayed significant positive correlations with the lowest oxygen saturation and MoCA score.

As known, the lower-ALFF area in the cluster of right precuneus and bilateral posterior cingulate gyrus is largely included in the default mode networks (DMNs).⁵¹ Similarly, Prilipko et al⁵² found that OSAs showed abnormal deactivation in the DMN during working-memory tasks and a significantly positive correlation between the deactivation of DMN regions and behavioral performance,⁵² suggesting that suppression of activity in the DMN plays a role in cognitive impairment. Beebe et al⁵³ also found, using sophisticated meta-analytic models, that OSA had a substantial impact on vigilance and executive functions but a negligible impact on intellectual and verbal function. Yaouhi et al⁵⁴ found that the glucose metabolic activity of precuneus and cingulate gyrus, which were not atrophic, was reduced in OSAs, compared with that in GSs, using a ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography method,⁵⁴ and that this functional impairment may have been caused partly by remote effects originating from morphologically impaired areas with decreased connectivity.⁵⁵ Furthermore, our study found a positive correlation between cerebral deactivation in parts

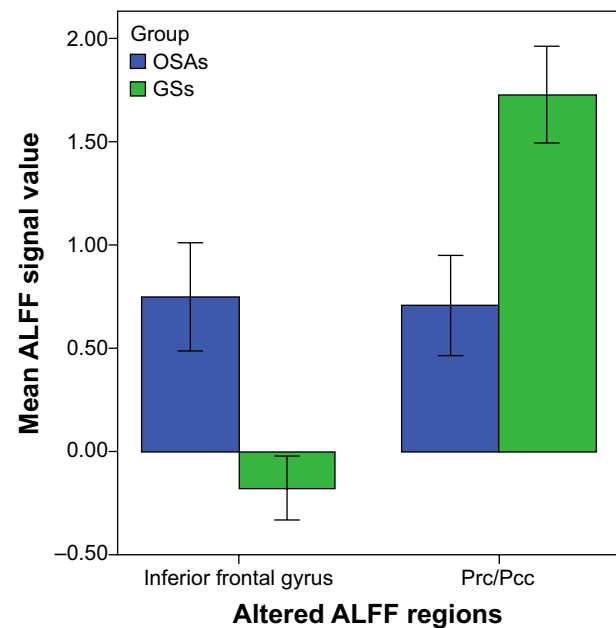
of regions of the DMN and the lowest oxygen saturation, suggesting that intermittent hypoxia may be an important factor for the DMN dysfunction in OSAs.

The cingulate area is activated by dyspnea,⁵⁶ breathlessness,⁵⁷ and emotion related to the need for air⁵⁸ and is involved in autonomic functions, including maintenance of blood pressure and salivary secretion, which suggests that the cingulate cortex has a complex and indirect relationship with the central networks that control respiration.^{59,60} Previous structural neuroimaging studies have found gray matter loss and white matter integrity reduction in the cingulate in OSAs.^{25,26} Joo et al²⁰ also found that OSAs had decreased gray matter concentrations in the cingulate cortex, which may explain the clinical manifestations such as respiratory, affective, and cardiovascular disturbances. Ayalon et al⁶¹

**Figure 1** Compared to GSs, OSAs showed altered ALFF areas.

Notes: The red color represents an higher-ALFF area (A), and the blue color represents a lower-ALFF area (B).

Abbreviations: GSs, good sleepers; OSAs, patients with obstructive sleep apnea; ALFF, amplitude of low-frequency fluctuation.

**Figure 2** Mean ALFF signal values for altered regional brain areas.

Notes: Compared with GSs, OSAs showed altered ALFF area in the left inferior frontal gyrus (0.75 ± 0.63 versus -0.17 ± 0.38 , respectively) and in the cluster of the right precuneus and bilateral posterior cingulate gyrus (0.71 ± 0.58 versus 1.72 ± 0.57 , respectively).

Abbreviations: GSs, good sleepers; OSAs, patients with obstructive sleep apnea; ALFF, amplitude of low-frequency fluctuation; Prc, precuneus; Pcc, posterior cingulate gyrus.

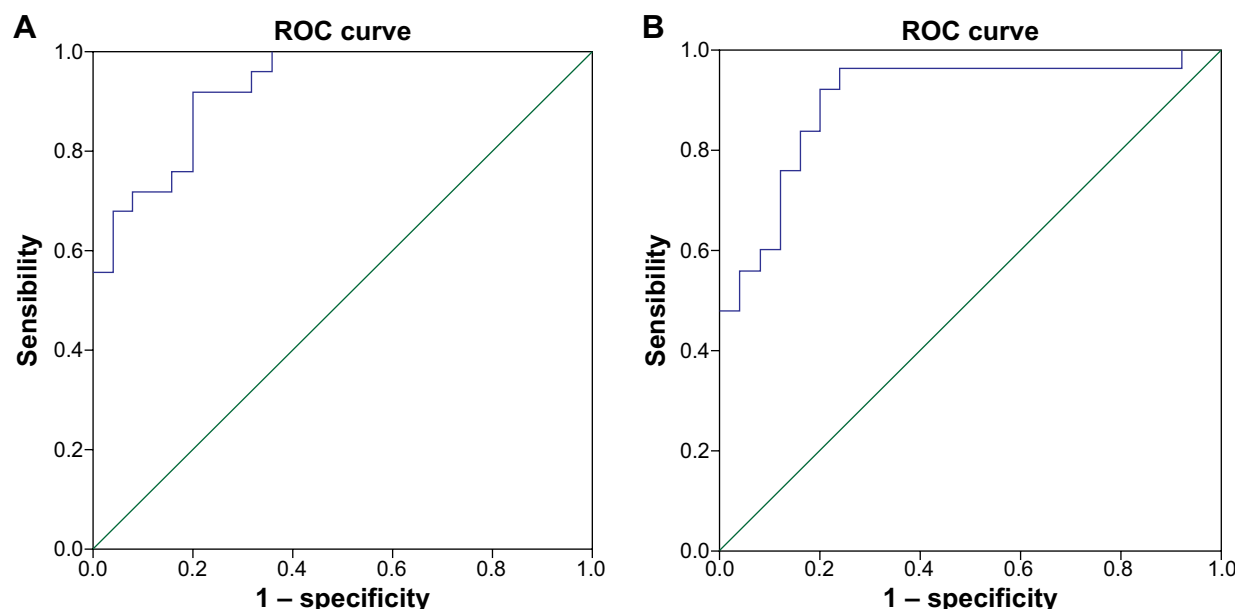


Figure 3 ROC curve analysis of mean ALFF signal values for altered regional brain areas.

Notes: (A) Depicts the ROC curve of left inferior frontal gyrus; ROC with AUC =0.93. (B) Depicts the ROC curve of cluster of right precuneus and bilateral posterior cingulate gyrus; ROC with AUC =0.90.

Abbreviations: AUC, area under the curve; ALFF, amplitude of low-frequency fluctuation; ROC, receiver operating characteristic.

found that OSAs showed decreased brain activation in left precentral gyrus, left anterior, and posterior cingulate, compared with control subjects, during an attention task. Similar results have been reported during valsalva maneuvers.⁶² These studies suggest that the cingulate gyrus may be particularly vulnerable to OSA-related impairment, independent of the specific cognitive challenge measured. In support of these functional and structural findings, our study found lower-ALFF areas in the posterior cingulate in OSAs compared with GSs. Moreover, a significant positive correlation between the lower-ALFF area and the MoCA score was observed in the OSAs. This brain-behavior relationship demonstrated that the abnormal properties of the posterior cingulate were associated with impaired cognitive function in OSAs.

The precuneus plays an important role in fundamental cognitive functioning, including episodic memory retrieval, visual-spatial imagery, self-processing, and consciousness.⁶³ Our previous study³⁸ found lower regional homogeneity area in the precuneus, which showed a significant negative correlation with sleep time, suggesting that decreased sleep time may be an important factor for dysfunction in the precuneus. In the current study, the lower-ALFF area in the right precuneus displayed significant positive correlation with MoCA score, suggesting that the abnormalities of the precuneus may be associated with a cognitive dysfunction.

Ayalon et al⁶⁴ found that compared with GSs, OSAs showed increased activity in the bilateral inferior frontal

gyrus, and a significant relationship between increased activation in the left inferior frontal gyrus and better immediate recall during a verbal learning task was found, suggesting an adaptive compensatory response. In support of this finding, in our study, OSAs showed higher ALFF in the left inferior frontal lobe, compared with GSs, which was consistent with previous studies on sleep deprivation⁶⁵ and healthy aging.⁶⁶

Conclusion

In conclusion, our findings suggest that the ALFF method may be a useful noninvasive imaging tool and a symbolic early biomarker for the detection of cerebral changes and for indexing of the changes of cognitive function, which may be helpful in the development of imaging biomarkers for the detection of cerebral changes. Furthermore, the abnormal spontaneous activity of the DMN region and the frontal lobe may be involved in the underlying pathophysiology of OSAs. However, there are several limitations that should be paid attention to. First, a larger sample size, as well as female and children populations, should be studied. Second, another group comparison, both before and after the treatment, will yield significant insight.

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Disclosure

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