Functional network alterations in adult obstructive sleep apnea: A resting-state fNIRS study

Zhao Mingming
People's Hospital of Guangxi Zhuang Autonomous region

Chen Wenhong
People's Hospital of Guangxi Zhuang Autonomous region

Mo Xiaoying
People's Hospital of Guangxi Zhuang Autonomous region

Yang Jianrong (zhaomm_md@163.com)
People's Hospital of Guangxi Zhuang Autonomous region

Howe Liu
Allen College

Shi Lingli
People's Hospital of Guangxi Zhuang Autonomous region

Ma Hongwu
People's Hospital of Guangxi Zhuang Autonomous region

Jiang Zhirong
People's Hospital of Guangxi Zhuang Autonomous region

Zhang Peiwen
Wuhan Znion Technology Co., Ltd

Research Article

Keywords: Obstructive sleep apnea, functional near infrared spectroscopy, resting-state functional connectivity, Graph theory

Posted Date: February 1st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2521017/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Study Objectives:
To evaluate brain network connectivity characteristics and complex network topology properties in adult with obstructive sleep apnea (OSA) based on functional near infrared spectroscopy (fNIRS).

Methods

Forty-five subjects including 22 with OSA and 23 healthy as the control were recruited for assessment of a 3-minute resting-state prefrontal cortex (PFC) activity with the fNIRS technique. Only the oxygenated hemoglobin(HbO2) signal was used to calculate resting-state functional connectivity (RSFC) and construct brain connection network. To better describe prefrontal connectivity, we also divided it into four types of connectivity (Short-1: intra-hemispheric connection within Regions of interest (ROIs); Short-2: intra-hemispheric connection between ROIs; Long-1: inter-hemispheric connection within ROIs; Long-2: inter-hemispheric connection between ROIs). We extracted the relevant indicators of brain network connection and the complex network based on graph theory, and then analyzed the correlation between the indicators and cognitive scale.

Results

Compared with the healthy control group, patients with OSA showed more chaotic connection patterns, weaker intra- and inter-hemispheric connection intensity, and lower integration efficient. Specifically, patients with OSA exerted significantly lower connection intensity and the total network edge numbers in all four connection types. Furthermore, the average correlation coefficient and global efficiency of brain network were positively correlated with Montreal Cognitive Assessment score.

Conclusions

The fNIRS-based brain functional connection and complex network topology properties in patients with OSA were significantly different from those in healthy subjects. Such differences based on the fNIRS technique could be considered as potential biomarkers for OSA diagnosis, assessment, and intervention.

Introduction

Obstructive sleep apnea-hypopnea syndrome(OSAHS) is a sleep-related disorder that causes chronic intermittent hypoxia and disturbed sleep structure due to repeated complete or partial obstruction of the upper airway during sleep leading to apnea and/or hypopnea [1]. The progression of OSA and its long-term nocturnal sleep hypoxemia, respiratory disorders and sleep fragmentation can lead to multiple
system and multiple organ dysfunction, and increase the risk of hypertension, cardio-cerebrovascular disease, type 2 diabetes and congestive heart failure.\textsuperscript{[2–5]} However, its neuropathological mechanism still remains unclear.

Functional near infrared spectroscopy (FNIRS) is a non-invasive and non-radiation optical imaging method, which can measure the real-time changes of oxygenated hemoglobin (HBO2), deoxyhemoglobin (HHb) and total hemoglobin (THb) in local brain regions\textsuperscript{[6]}. The changes in hemoglobin concentration reflect the activation of cerebral cortex, the change of brain network connection and other information. Thus, the fNIRS is valuable in the evaluation of disease severity, guidance of treatment, and assessment of curative effect\textsuperscript{[7,8]}.

As far as we know, up to date there is no literature yet on the application of FNIRS in the evaluation of resting-state brain functional network characteristics of OSA. Therefore, in this study, we used FNIRS to construct the resting brain functional network connection, and analyze the brain complex network based on graph theory in patients with OSA in order to explore the potential brain mechanism of OSA, and provide some imaging evidence for evaluation and treatment guidance for OSA patients.

**Materials And Methods**

Twenty-five patients with OSA were initially recruited, but 3 of them were excluded due to poor data quality (see details in Section 2.3.1), resulting in a total of twenty-two patients (20 males and 2 females, mean age = 41.23 ± 12.08) for data analysis. In addition, twenty-three healthy subjects as controls (17 males and 6 females, mean age = 36.96 ± 7.92) matched in age, sex and education were recruited. All subjects in both groups were right-handed and had no history of any neurological diseases, including brain injury. All patients were recruited from the hospital where the principle investigator (PI) works. The normal controls were hospital staff and volunteers in the local community. The OSA patients were diagnosed with the International Classification of Sleep Disorders-Third Edition (ICSD-3) criteria\textsuperscript{[9]}.

Prior to the experiments, cognitive ability was evaluated with the Montreal Cognitive Assessment (MoCA)\textsuperscript{[10]}. All subjects were informed the experimental procedure in detail and signed their informed consent forms. Prior to the measurement, each individual in both groups was asked to sit on a comfortable chair in a quiet room, close their eyes, stay relaxed without falling sleep and with any body movement during the entire 3-minute experiment. Experimental protocol was approved by the Ethic Committee of the PI's hospital.

2.2 NIRS Measurement

The 37 multi-channel FNIRS instrument (BS-3000, Wuhan Znion Technology Co., Ltd., Wuhan, China) measures the concentration changes of hemoglobin in prefrontal cortex using two wavelengths (690 and 830nm) of infrared light. Each channel consists of a source-detector pair at a distance of 3 cm and were
placed with reference to the 10–20 system (Channel 22 is located at Fpz.)\textsuperscript{[11]}. 16 sources and 16 detectors constitute a total of 37 channels. The 37-channel placement is shown in Fig. 1a.

In order to normalize the fNIRS channel, we applied a 3D digitizer (NirMap, Wuhan Znion Technology Co., Ltd., Wuhan, China) to record the exact spatial coordinates of 4 reference points (Nz, Cz, AL and RL) and 32 probes. Then the 37 channels were converted to an estimated Montreal Neurological Institute (MNI) space\textsuperscript{[12]} by NIRS-SPM\textsuperscript{[13]}. To analyze the different types of intra-hemispheric and inter-hemispheric connectivities\textsuperscript{[14]}, we needed to identify different regions of interest (ROIs). According to the automatic anatomical labeling (AAL) template\textsuperscript{[15]}, each channel was projected to cortical surface via NIRS_SPM\textsuperscript{[13]}. Then the 37 channels were divided into six ROIs based on the maximum overlap probability: the left and right inferior frontal gyrus (IFG-L and IFG-R, red label in Fig. 1), left and right middle frontal gyrus (MFG-L and MFG-R, green label in Fig. 1), left and right superior frontal gyrus (SFG-L and SFG-R, blue label in Fig. 1). And three channels in mid-hemisphere line were excluded (Grey label in Fig. 1).

2.3 Data analysis

2.3.1 Data pre-processing

FC-NIRS, a MATLAB-based toolbox was used to analyze the fNIRS data\textsuperscript{[16]}. Firstly, the raw optical intensity was converted to optical density (OD) similar to Homer software\textsuperscript{[17]}. Secondly, changes in relative concentration of oxygenated hemoglobin (HbO2), deoxygenated hemoglobin (HbR) and a total of hemoglobin (HbT) were calculated according to modified Beer-Lambert Law\textsuperscript{[18]}. The concentration signal was then filtered using a band-pass filtering with range 0.01-0.1Hz to remove artifacts such as baseline drift and cardiac interference\textsuperscript{[19]}. A spline interpolation method\textsuperscript{[20]} was used to reduce the motion artifacts. Specifically, the motion-induced artifacts were detected by calculating the standard deviation within 2-second sliding time windows. Standard deviation values larger than five standard deviations away from the mean are regarded as artifacts and were further modeled via a cubic spline interpolation, which was subtracted from the original signal. Finally, in order to remove the possible effects of initial instability which came from machine and participants, we removed the first 15 seconds data. The remaining 165 seconds data were baseline corrected using first 5 seconds data and subsequently analyzed for functional connectivity analysis. It is worth noting that we calculated the coefficient of variation (CV) values of the entire data for each channel to ensure signal quality\textsuperscript{[21]}. Any channel with a CV value greater than 35% was marked as bad channel. When the number of bad channel exceeds 20% of the total, the participant was eliminated. With this said in this study, three patients data were excluded.

2.3.2 Resting-state functional connectivity
Only the HbO2 signal was used to calculate resting-state functional connectivity (RSFC) in this study. All RSFC analysis was performed using FC-NIRS\cite{16}. To visualize brain network in 3D space, we used BrainNet Viewer to show the edge of the networks\cite{22}. As a conventional method, Pearson's correlation coefficient was calculated in any possible channel pair, which represented the strength of RSFC. This generated a correlation matrix for each participant.

The average FC matrix between patients and normal controls group was compared, followed by analyzing the intra-hemispheric and inter-hemispheric connectivities. After the FC matrix according to the ROI (IFG-L, MFG-L, SFG-L, IFG-R, MFG-R and SFG-R, see details in Fig. 2a) was rearranged, we defined four interest connectivity types\cite{14}: 1) the short-distance connectivity 1 for the intra-hemispheric connectivity within each ROI (Fig. 2b); 2) the short-distance connectivity 2 for the intra-hemispheric connectivity between different ROIs including IFG-L to MFG-L, IFG-L to SFG-L, MFG-L to SFG-L, IFG-R to MFG-R, IFG-R to SFG-R, MFG-R to SFG-R (Fig. 2c); 3) the long-distance connectivity 1 for the inter-hemispheric connectivity between symmetrical ROIs including IFG-L to IFG-R, MFG-L to MFG-R, SFG-L to SFG-R (Fig. 2d); and 4) the long-distance connectivity 2 for the inter-hemispheric connectivity between asymmetrical ROIs including IFG-L to MFG-R, IFG-L to SFG-R, MFG-L to SFG-R, IFG-R to MFG-L, IFG-R to MFG-R to SFG-L and MFG-R to SFG-L (Fig. 2e). These four connectivity types were also presented in FC matrix (Fig. 3A).

In this part, two metrics, the average correlation coefficient and the total network edge numbers were measured as the strength of RSFC. The average correlation coefficient was defined as the mean values of correlation coefficient in different connectivity types and ROIs. For this, we first transformed the r value to z value using Fisher's r-to-z transformation in each channel pair. Then, we averaged all the z values in the chosen connectivity type or ROI. The total network edge numbers were calculated as the connection numbers in the network within different thresholds. Specifically, the channel was defined as “node” of network, and the correlation coefficient between any channel pair as the “edge” of network. In addition, we set a threshold value \( T \) to binarize the correlation matrix (0 or 1). The 0 indicates that the \( r \) value was smaller than \( T \) and there was no significant correlations and no edge in that channel pair. In contrast, the 1 indicates that the \( r \) value was larger than or equal to \( T \) and there was significant correlation and an edge in that channel pair. In this study, the \( T \) value of the threshold was set at 0.4-0.9 and a step size of 0.05\cite{14}. Lastly, total network edge numbers were calculated for four connectivity types (Fig. 5) and different ROIs. Notably, we found there was almost no significant correlation and edge in average FC matrix for the patient group when the \( T \) reaches 0.65 (Supplementary Fig.S1). We therefore mainly analyzed the data with a threshold value \( T \) of 0.4, 0.5 and 0.6.

To further characterize the topological properties of the brain network, we performed a modern graph-theoretical analysis\cite{23–25}. The metrics used in this study included global and local efficiency\cite{26}, and clustering coefficient\cite{27}. In brief, the global efficiency reflected the average efficiency of information sharing in entire network, representing the network integration. The local efficiency reflected the efficiency
of information sharing in local network. The clustering coefficient reflected the ratio of connections existing between one node and its nearest neighbors, representing the network segregation\cite{28, 29}.

### 2.3.3 Statistical Analysis

Statistical analysis was performed with IBM SPSS Version 22. Age, educational level, and the differences of average correlation coefficient after Fisher r-to-z transformation between two groups were compared with simple t-test. The sex difference was statistical quantified using chi-square test. The MoCA scores, the network edge number, global efficiency, local efficiency, and clustering coefficient between two groups were assessed using the Mann Whitney U test. The statistical tests were corrected for multiple comparisons using Benjamini-Hochberg correction\cite{30} to control the false discovery rate (FDR).

Also, the relationships between global brain network measures (average correlation coefficient, edge numbers, global efficiency, local efficiency and clustering coefficient) and clinical score (MoCA) in both groups were evaluated to further validate the clinical values. The partial correlation between network metrics and clinical score regarding education level and age as control variables was assessed with consideration of the potential effect of age and education level on MoCA score.

### Results

#### 3.1 Demographic and Clinical Rating Score

The results showed that there was no significant difference in age, gender and education level between the two groups ($P > 0.05$). And there was significant difference in MoCA scores between the two groups ($P < 0.05$). Results are presented in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HC(n = 23)</th>
<th>OSA(n = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>36.96 ± 7.92</td>
<td>41.23 ± 12.08</td>
<td>0.166</td>
</tr>
<tr>
<td>Gender(M/F)</td>
<td>17/6</td>
<td>20/2</td>
<td>0.243(^a)</td>
</tr>
<tr>
<td>Education(years)</td>
<td>15.74 ± 2.80</td>
<td>14.77 ± 3.16</td>
<td>0.283</td>
</tr>
<tr>
<td>MoCA</td>
<td>28.32 ± 1.78</td>
<td>23.60 ± 4.33</td>
<td>0.000(^b)</td>
</tr>
</tbody>
</table>

\(^a\) chi-square test; \(^b\) Mann Whitney U test; HC healthy control; OSA obstructive sleep apnea

#### 3.2 Correlation matrix and connection network
Figures 3A and 3B show the functional connectivity matrix of HC and OSA, and the functional connectivity networks under different thresholds, respectively. The functional Brain Network Connectivity patterns of OSA are similar to that of HC. Specifically, both the intra-hemispheric and inter-hemispheric connections within MFG and SFG, as well as between MFG and SFG are strong. The intra-hemispheres and inter-hemispheres connections within IFG are also strong, while those connection between IFG and other brain regions are weak. Although the connection pattern was similar, the overall connection in OSA patients were weaker than that in HC. When the threshold was set to 0.65, there was almost no effective connection in the patient group (see Supplementary Fig. S2).

### 3.3 Functional connectivity strength

There was a significant difference between groups in the overall average functional connectivity strength in the prefrontal cortex (Group, $pFDR = 0.08$) (Table 2 and Fig. 4). For each of these four functional connections, the z-score of the patient group are significantly lower than that of the control group (Table 2). For ROI pairs comparisons, six ROI pairs showed significant differences in HbO2 between groups, all six ROI pairs showed that the z-score of the patient were lower than that of the healthy group, including S1 MFG mask ($pFDR = 0.021$), S2 IFG MFG mask ($pFDR = 0.021$), S2 IFG SFG mask ($pFDR = 0.021$), S2 MFG SFG mask ($pFDR = 0.021$), L2 IFG MFG L mask ($pFDR = 0.021$), L2 IFG SFG L mask ($pFDR = 0.032$). For the rest of average functional connectivity strength of other ROI pairs, there were no significant differences between the groups ($pFDR > 0.05$) (Supplementary Fig. S3).

Table 2 Comparison between groups of average functional connectivity strength of different connection types
### Table

<table>
<thead>
<tr>
<th>Functional types</th>
<th>connection</th>
<th>Mean Fisher-transformed z-scores of correlation coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>OSA</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td>0.510±0.182</td>
<td>0.344±0.216</td>
</tr>
<tr>
<td>S1 mask</td>
<td></td>
<td>0.696±0.216</td>
<td>0.503±0.247</td>
</tr>
<tr>
<td>S2 mask</td>
<td></td>
<td>0.475±0.175</td>
<td>0.315±0.211</td>
</tr>
<tr>
<td>L1 mask</td>
<td></td>
<td>0.588±0.225</td>
<td>0.412±0.249</td>
</tr>
<tr>
<td>L2 mask</td>
<td></td>
<td>0.412±0.179</td>
<td>0.261±0.210</td>
</tr>
<tr>
<td>S1 IFGL mask</td>
<td></td>
<td>0.571±0.311</td>
<td>0.465±0.265</td>
</tr>
<tr>
<td>S1 MFGL mask</td>
<td></td>
<td>0.775±0.298</td>
<td>0.584±0.352</td>
</tr>
<tr>
<td>S1 SFG mask</td>
<td></td>
<td>0.721±0.265</td>
<td>0.627±0.449</td>
</tr>
<tr>
<td>S1 IFGR mask</td>
<td></td>
<td>0.729±0.319</td>
<td>0.478±0.375</td>
</tr>
<tr>
<td>S1 MFG mask</td>
<td></td>
<td>0.734±0.310</td>
<td>0.407±0.348</td>
</tr>
<tr>
<td>S1 SFG mask</td>
<td></td>
<td>0.666±0.253</td>
<td>0.490±0.279</td>
</tr>
<tr>
<td>S2 IFGL MFGL mask</td>
<td></td>
<td>0.413±0.223</td>
<td>0.353±0.187</td>
</tr>
<tr>
<td>S2 IFGL SFGL mask</td>
<td></td>
<td>0.256±0.172</td>
<td>0.224±0.224</td>
</tr>
<tr>
<td>S2 MFGL SFGL mask</td>
<td></td>
<td>0.672±0.232</td>
<td>0.520±0.368</td>
</tr>
<tr>
<td>S2 IFGR MFG mask</td>
<td></td>
<td>0.484±0.230</td>
<td>0.269±0.218</td>
</tr>
<tr>
<td>S2 IFGR SFGR mask</td>
<td></td>
<td>0.349±0.227</td>
<td>0.139±0.251</td>
</tr>
<tr>
<td>S2 MFG SFGR mask</td>
<td></td>
<td>0.686±0.275</td>
<td>0.388±0.310</td>
</tr>
<tr>
<td>L1 IFG mask</td>
<td></td>
<td>0.490±0.282</td>
<td>0.331±0.299</td>
</tr>
<tr>
<td>L1 MFG mask</td>
<td></td>
<td>0.633±0.290</td>
<td>0.422±0.315</td>
</tr>
<tr>
<td>L1 SFG mask</td>
<td></td>
<td>0.665±0.248</td>
<td>0.516±0.311</td>
</tr>
<tr>
<td>L2 IFGL MFG mask</td>
<td></td>
<td>0.311±0.242</td>
<td>0.194±0.209</td>
</tr>
<tr>
<td>L2 IFGL SFGR mask</td>
<td></td>
<td>0.234±0.217</td>
<td>0.168±0.188</td>
</tr>
<tr>
<td>L2 MFGL SFGR mask</td>
<td></td>
<td>0.588±0.264</td>
<td>0.437±0.290</td>
</tr>
<tr>
<td>L2 IFGR MFG mask</td>
<td></td>
<td>0.448±0.227</td>
<td>0.227±0.264</td>
</tr>
<tr>
<td>L2 IFGR SFGR mask</td>
<td></td>
<td>0.325±0.184</td>
<td>0.146±0.252</td>
</tr>
<tr>
<td>L2 MFG SFGR mask</td>
<td></td>
<td>0.581±0.245</td>
<td>0.414±0.316</td>
</tr>
</tbody>
</table>

* Significant difference between the two groups after multiple comparison correction controlled by FDR.

S1: Short-1; S2: Short-2; L1: Long-1; L2: Long-2; L left; R right; IFG inferior frontal gyrus; MFG middle frontal gyrus; SFG superior frontal gyrus.

### 3.4 Number of functional connection edges

The edges represent the connections between the nodes. Each small circle in Fig. 5A represents the averaged edge number for each participant at a certain threshold value. With the threshold increasing, the number of effectively connected edges for OSA and HC decreases. It is worth noting that the edges number in OSA was lower than that in HC group at different thresholds in both overall and four types. The edge numbers for OSA was significantly lower than HC at a threshold of 0.5 in all four types (Fig. 5C) (Short-1 $pFDR = 0.008$, Short-2 $pFDR = 0.004$, Long-1 $pFDR = 0.016$, Long-2 $pFDR = 0.008$). In order to avoid the bias caused by threshold, we also presented the results with a threshold of 0.4 and 0.6 (Supplementary Fig.S4). To more specifically reveal the differences between OSA and HC in detail, we investigated the connectivities for different ROI pairs at a threshold of 0.5 (Supplementary Fig.S5). The Short-1 in MFG-R ($pFDR = 0.000$), Short-2 connectivity in MFG-R to SFG-R ($pFDR = 0.011$) and IFG-R to MFG-R ($pFDR = 0.014$), and Long-2 connectivity in IFGR to MFGL ($pFDR = 0.042$) was significantly decreased in OSA than HC (see Fig. 5C). At the threshold of 0.4 and 0.6, we found the similar results (Supplementary Fig.S6).

### 3.5 Graph-based Analysis

The global efficiency, local efficiency and clustering coefficient were higher in the HC group than in the OSA group at different thresholds (Fig. 6A-6C). At the threshold of 0.5, global efficiency (Fig. 6D) showed
significantly differences ($pFDR = 0.016$) between two groups while local efficiency (Figure. 6E, $pFDR = 0.058$) and cluster coefficient (Figure. 6F, $pFDR = 0.073$) showed no difference.

### 3.6 Relationships between Brain Network Measures and MoCA score

The partial correlation between network metrics and MoCA score controlling the effects of education level and age was assessed to identify how the mental status is associated with the brain networks. As shown in Table 3 and Fig. 7, the MoCA score was correlated with both the average connectivity coefficient and the global efficiency, but, seemed not to correlate with the edge number, local efficiency and cluster coefficient.

Table 3

<table>
<thead>
<tr>
<th>Network measures</th>
<th>MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>P-value</td>
</tr>
<tr>
<td>Mean correlation coefficient</td>
<td>0.336</td>
</tr>
<tr>
<td>Average edge numbers</td>
<td>0.302</td>
</tr>
<tr>
<td>Global efficiency</td>
<td>0.339</td>
</tr>
<tr>
<td>Local efficiency</td>
<td>0.306</td>
</tr>
<tr>
<td>Clustering coefficient</td>
<td>0.266</td>
</tr>
</tbody>
</table>

In summarize, in this study, we first briefly compared the average functional connection mode and strength between OSA and HC. In the second step, we used the average correlation coefficient and the number of network edges to measure the RSFC strength of the two groups of subjects with four connection types. The third step was to analyze the brain connection network based on graph theory, and the correlation between complex network index and clinical index was analyzed. Compared with the healthy control group, patients with OSA showed more chaotic connection patterns, weaker intra- and inter-hemispheric connection intensity, and lower integration efficient. Specifically, patients with OSA exerted significantly lower connection intensity and the total network edge numbers in all four connection types. Furthermore, the average correlation coefficient and global efficiency of brain network were positively correlated with MoCA Montreal Cognitive Assessment score.

### Discussion

FNIRS is a non-invasive and convenient optical imaging technology, which can measure the changes of oxygenated hemoglobin (HbO2) and deoxyhemoglobin (HbR) in cerebral cortex in real time, so it can provide information about the state of brain activity. It is suitable for a wide range of people and has good applicability for special people, such as people with metal implants (cardiac pacemakers, cochlear implants, etc.) are not affected, and are widely used in neurovascular diseases, mental diseases, pediatrics and other fields\[7,8,31–33\]. Compared with HbR, HbO2 has a better signal-to-noise ratio and a higher correlation with blood oxygen level-dependent (BOLD) signals\[34,35\]. In this study, the brain network measures was only based on HbO2 signals. The Resting-state FNIRS has the advantage of simple and fast data acquisition, the analysis based on its raw data can obtain information such as brain
activity and functional connection, which can help to diagnose and determine the treatment plan. Previous resting-state functional magnetic resonance imaging (rs-fMRI) studies have found that OSA patients have a wide range of spontaneous activity abnormalities in brain regions, and abnormal functional connections in emotional, cognitive, executive, sensorimotor related brain regions\[^{36,37}\]. However, to the best of our knowledge, up to date, no study has been conducted in application of FNIRS in patients with OSA to explore the characteristics of brain functional connections and topological properties of brain complex networks in such a population.

First of all, we observed that the resting-state functional connectivity network patterns of the PFC in OSA patients were similar to those in normal subjects, but compared with the healthy control group, the brain network connection mode of PFC in OSA patients was more chaotic, and the intraregional connectivity, intrahemispheric connectivity, and interhemispheric connectivity were all lower than those in normal controls.

The functional connection defect of PFC in patients with OSA is related to the dysfunction of spontaneous and instinctive activity in the resting state, and the decrease of connection strength may explain the decrease of related function\[^{38}\]. There were significant differences between the two groups in overall and four functional connectivity types of connectivity coefficients. Under different thresholds, the number of network connection edges of OSA patients was lower than that of normal people, and there was a significant difference between groups at a threshold of 0.5. It is worth noting that there was a significant difference in the average functional connection coefficient of 6 ROI pairs under the four connection types, which are S1-MFGR, S2-IFGR-MFGR, S2-IFGR-SFGR, S2-MFGR-SFGR, L2-IFGR-MFGL and L2-IFGR-SFGL respectively, the results suggest that the different brain regions of short-distance connections may be lateralized. We speculated that the effect of OSA on cerebral perfusion in the right side was greater than that in the left side. Previous fMRI-based studies have shown that there is a significant correlation between changes in the functional connection network of the right frontal lobe and the severity of OSA\[^{39}\], larger samples need to be included to further confirm the asymmetry of cerebral hemodynamic changes and brain functional connection networks in patients with OSA. This study revealed decreased connectivity of the prefrontal cortex in patients with OSA, reflecting impaired blood perfusion and hemodynamic abnormalities. Combined with previous structural and functional nuclear magnetic resonance studies of OSA, we speculate that abnormal functional connection in patients with OSA is closely related to neurovascular lesions in OSA.

Complex network analysis based on graph theory can be used to describe complex brain functional network systems and explore the topological properties of brain functional networks\[^{40}\]. We compared the global efficiency, local efficiency and clustering coefficient of the two groups of subjects at different thresholds, and found that the global efficiency, local efficiency and clustering coefficient of PFC in OSA patients decreased. The comparison between groups showed that there was a significant difference in global efficiency, and the results are consistent with previous results based on fMRI\[^{41}\]. Global efficiency represents the total capacity for parallel processing of information and integrated processing\[^{42}\]. Local
efficiency indicates that information is effectively shared within the local network based on effectually segregated information processing\cite{43}. Clustering coefficient generally represents a summary of the local interactions between a particular ROI and its neighboring ROIs, demonstrating the segregation within the brain network\cite{44}. In this study, we found that the global efficiency of PFC in OSA group was significantly decreased, suggesting that the global information transmission efficiency was decreased and functional integration was impaired in patients with OSA. Furthermore, we observed that the local efficiency and clustering coefficient of the OSA group were both lower than those of the normal group, although there was no significant difference between the groups. The supplementary Fig.S5 shows the average global efficiency, local efficiency, and clustering coefficient of the two groups of subjects at different thresholds, with a step size of 5% and a threshold range of 40–90%. Our research demonstrates that the global brain network properties of prefrontal cortex in patients with OSA are lower than those in healthy controls, and the brain network in patients with OSA has lower information transmission efficiency, integration and separation. PARK et al. used graph theory to study the topological properties of the whole-brain FC and brain network in OSA patients based on fMRI, and confirmed that the extensive functional connectivity alteration in the whole brain of OSA are related to the lower integration efficiency of the brain network and the reduction of regional topological properties. They believe that OSA alteration in the FC further lead to disruption of topological properties, especially the integrative function of brain network organization\cite{38,45}. We speculate that long-term nocturnal hypoxemia and sleep fragmentation in patients with OSA lead to changes in cerebral hemodynamics, which lead to abnormal functional connections of the brain network, changes in the topological properties of the brain complex network, and further affect the whole brain function. The results of brain network connectivity index and graph theory measurement are still difficult to explain from the point of view of behavior or pathophysiology, but the analysis of patients' brain complex network may be a potential biomarker for the diagnosis and treatment of OSA\cite{38}.

Several resting-state fMRI studies of OSA have shown that chronic exposure to oxidative stress, intermittent hypoxia, hypocapnia, and sleep fragmentation, which are major causes of brain damage in OSA, may lead to global and local networks in the PFC attribute changes that further lead to cognitive impairment\cite{36,46,47}. In order to better understand the relationship between fNIRS measurement of OSA and disease, it is necessary to study the relationship between direct physiological index of OSA and fNIRS measurement. We used partial correlation analysis to examine correlations between network metrics (average correlation coefficient, edge numbers, global efficiency, local efficiency and clustering coefficient) and the cognitive scale (MoCA) for all subjects, using age and education as control variables, to assess the reliability and clinical value of brain network measures. The results showed that the mean correlation coefficient with global efficiency was statistically significant with MoCA score, suggesting a correlation between brain network measurements and clinical score, thus demonstrating the clinical value of these biomarkers in the diagnosis and treatment of OSA. There was no significant correlation between other brain network indexes and clinical score, the lack of significance could be possibly accounted for the relatively small sample size. In the future, more comprehensive research should be carried out and the research sample should be expanded to verify these network indicators and draw reliable conclusions.
Limitation

This study was subject to the following limitations. Male patients predominated in the population (82.22%), although we adjusted for sex in our analyses, it is not entirely possible to eliminate sex effects as confounders. The sample size of this study is small and it is a single-center study, there was no subgroup analysis by complication, we should analyze a wider range of cohorts in the future in order to verify and expand the current research results. And a more detailed neuropsychological assessment questionnaire needs to be added in the future to evaluate different cognitive changes for further analysis. In terms of measurement technology, fNIRS has limited measurement depth and spatial resolution, our results should be interpreted with caution.

Conclusion

In this study, resting-state fNIRS imaging was used to assess the complexity of spontaneous brain signals in patients with OSA and the relationship between these signals and cognitive performance. Our results show that the fNIRS-based brain functional connection and complex network topology properties of OSA patients were significantly different from those of healthy controls. The PFC of OSA patients has a more disorganized brain network connectivity pattern, with significantly lower intraregional and interhemispheric connectivity, and lower integration efficiency compared with healthy controls. The average correlation coefficient and global efficiency of brain network were positively correlated with MoCA score. Thus, we can conclude that the analysis of brain function connection and complex network topology attributes based on fNIRS may be used as potential biomarkers for OSA diagnosis, treatment and disease assessment.

Declarations

Funding

This work was supported by National Natural Science Foundation of China (Grant no. 82260021); Natural Science Foundation of Guangxi Zhuang Autonomous region in China (Grant no.2021JJB140634); Project of Guangxi Science and Technology Department(Grant no. A22096018).

Data Availability Statement

Data available on request from the authors.

References


5. AS Jordan DGM, Malhotra A. Adult obstructive sleep apnoea. The Lancet. 2014.


Figures
Figure 1

37 channels were divided into six ROIs based on the maximum overlap probability: left and right inferior frontal gyrus (IFG-L and IFG-R, red label), left and right middle frontal gyrus (MFG-L and MFG-R, green label), left and right superior frontal gyrus (SFG-L and SFG-R, blue label). And three channels in mid-hemisphere line were excluded (Grey label). The frontal (Fig. 1a), right lateral (Fig. 1b) and left lateral view (Fig. 1c) were shown.
The four connectivity type was presented in FC matrix (Fig. 2a). We defined four interest connectivity type: Short-distance connectivity 1 (Short-1) was the intra-hemispheric connectivity within each ROI (Fig. 2b); Short-distance connectivity 2 (Short-2) was the intra-hemispheric connectivity between different ROIs: IFG-L to MFG-L, IFG-L to SFG-L, MFG-L to SFG-L, IFG-R to MFG-R, IFG-R to SFG-R, MFG-R to SFG-R (Fig. 2c); Long-distance connectivity 1 (Long-1) was the inter-hemispheric connectivity between symmetrical ROIs: IFG-L to IFG-R, MFG-L to MFG-R, SFG-L to SFG-R (Fig. 2d); Long-distance connectivity 2 (Long-2) was the inter-hemispheric connectivity between asymmetrical ROIs: IFG-L to MFG-R, IFG-L to SFG-R, MFG-L to SFG-R, IFG-R to MFG-L, IFG-R to SFG-L and MFG-R to SFG-L (Fig. 2e).
Figure 3

A. Grouped-averaged correlation matrix maps of the PFC for the HC and OSA. Each pixel in the correlation matrix maps has the Pearson correlation coefficient $r$ value of the responding channel pair in each ROI. L is the left hemisphere, and R is right hemisphere. IFG: The inferior frontal gyrus; MFG: The middle frontal gyrus; SFG: the superior frontal gyrus. B. Functional connectivity networks under different thresholds. Nodes colored with blue, green, and red refer to different ROIs' channels, and the black line between two nodes indicates an edge (valid connection at a specific threshold) between these two channels.
Figure 4

The histogram summarizes the corresponding correlation coefficients. A. Comparison of average correlation coefficients of four connection types. The blue bar represents the normal group, the red bar represents the OSA group. B. For ROI pairs comparisons, six ROI pairs in Short-1, Short-2 and Long-2 connectivity showed significant differences in HbO2 between groups, all six ROI pairs showed that the z-score of the OSA patient were lower than that of HC. *: $p_{FDR} < 0.05$. 

![Diagram](image-url)
**Figure 5**

A. Four clusters of functional connectivities among OSA and HC. Each small circle represents the averaged edge number for each participant at a certain threshold value. Blue and red curves represent the averaged edge numbers at different threshold values of OSA and the HC, respectively. 5B. The comparison results of the average number of connected edges of the four connection types under the threshold of 0.5. The blue bar represents the normal group, the red bar represents the OSA group. 5C. Four ROI pairs with significant differences between groups under 0.5 threshold. *: $p_{FDR} < 0.05$.

**Figure 6**

A. Global efficiency scatter plots, Each data point represent the global efficiency for each participant at a certain threshold value. Blue and red curves represent the global efficiency at different threshold values of OSA and the HC, respectively. B. Local efficiency scatter plots. C. Clustering efficiency scatter plots. D. Global efficiency bar graphs. The blue bar represents the normal group. The red bar represents the OSA group. E. Local efficiency bar graphs. F. Clustering efficiency bar graphs. *: $p_{FDR} < 0.05$. 
Figure 7

Correlation Analysis Chart between brain Network Measurement and MoCA.