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Original Article

Alterations of Limbic Structure Volumes in Patients with Obstructive Sleep Apnea

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ABSTRACT: ***Objectives:*** We investigated the change in limbic structure volumes and intrinsic limbic network in patients with obstructive sleep apnea (OSA) compared to healthy controls. ***Methods:*** We enrolled 26 patients with OSA and 30 healthy controls. They underwent three-dimensional T1-weighted magnetic resonance imaging (MRI) on a 3 T MRI scanner. The limbic structures were analyzed volumetrically using the FreeSurfer program. We examined the intrinsic limbic network using the Brain Analysis with Graph Theory program and compared the groups' limbic structure volumes and intrinsic limbic network. ***Results:*** There were significant differences in specific limbic structure volumes between the groups. The volumes in the right amygdala, right hippocampus, right hypothalamus, right nucleus accumbens, left amygdala, left basal forebrain, left hippocampus, left hypothalamus, and left nucleus accumbens in patients with OSA were lower than those in healthy controls (right amygdala, 0.102 vs. 0.113%, $p = 0.004$; right hippocampus, 0.253 vs. 0.281%, $p = 0.002$; right hypothalamus, 0.028 vs. 0.032%, $p = 0.002$; right nucleus accumbens, 0.021 vs. 0.024%, $p = 0.019$; left amygdala, 0.089 vs. 0.098%, $p = 0.007$; left basal forebrain, 0.020 vs. 0.022%, $p = 0.027$; left hippocampus, 0.245 vs. 0.265%, $p = 0.021$; left hypothalamus, 0.028 vs. 0.031%, $p = 0.016$; left nucleus accumbens, 0.023 vs. 0.027%, $p = 0.002$). However, there were no significant differences in network measures between the groups. ***Conclusion:*** We demonstrate that the volumes of several limbic structures in patients with OSA are significantly lower than those in healthy controls. However, there are no alterations to the intrinsic limbic network. These findings suggest that OSA is one of the risk factors for cognitive impairments.

RÉSUMÉ : Modifications du volume de structures limbiques chez des patients atteints d'apnée obstructive du sommeil. ***Objectif :*** L'étude visait à évaluer le changement de volume des structures limbiques et du réseau limbique intrinsèque chez des patients souffrant d'apnée obstructive du sommeil (AOS) comparativement à des témoins en bonne santé. ***Méthode :*** Au total, 26 patients souffrant d'AOS et 30 témoins en bonne santé ont participé à l'étude. Ils ont tous passé une IRM en trois dimensions, pondérée en T1, au moyen d'un appareil Tesla 3. Il y a eu une analyse volumétrique des structures limbiques à l'aide du programme FreeSurfer, et un examen du réseau limbique intrinsèque à l'aide du programme Brain Analysis with Graph Theory, après quoi il y a eu une comparaison du volume des structures limbiques et du réseau limbique intrinsèque entre les groupes. ***Résultats :*** Des différences importantes du volume de certaines structures limbiques ont été observées entre les groupes. Ainsi, le volume de l'amygdale droite, de l'hippocampe droit, de l'hypothalamus droit, du noyau accumbens droit, de l'amygdale gauche, du prosencéphale basal gauche, de l'hippocampe gauche, de l'hypothalamus gauche et du noyau accumbens gauche était plus petit chez les patients atteints d'AOS que chez les témoins en bonne santé (amygdale droite : 0,102 contre [c.] 0,113 %; $p = 0{,}004$; hippocampe droit : 0,253 c. 0,281 %; $p = 0{,}002$; hypothalamus droit : 0,028 c. 0,032 %; $p = 0{,}002$; accumbens nucléaire droit : 0,021 c. 0,024 %; $p = 0{,}019$; amygdale gauche : 0,089 c. 0,098 %; $p = 0{,}007$; prosencéphale basal gauche : 0,020 c. 0,022 %; $p = 0{,}027$; hippocampe gauche : 0,245 c. 0,265 %; $p = 0{,}021$; hypothalamus gauche : 0,028 c. 0,031 %; $p = 0{,}016$; accumbens nucléaire gauche : 0,023 c. 0,027 %; $p = 0{,}002$). Par contre, il n'y avait de différence importante entre les groupes quant aux mesures du réseau. ***Conclusion :*** Les résultats de l'étude ont démontré que le volume de plusieurs structures limbiques était passablement plus petit chez les patients atteints d'AOS que chez les témoins en bonne santé. Par contre, aucune modification du réseau limbique intrinsèque n'a été observée. Aussi les données recueillies donnent-elles à penser que l'AOS est l'un des facteurs de risque de troubles cognitifs.

Keywords: Limbic system; Obstructive sleep apnea; Volume

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Introduction

Obstructive sleep apnea (OSA) is characterized by episodic upper airway collapse, which is sleep state dependent, resulting in periodic reductions or cessations in ventilation, hypoxia, hypercapnia, or arousals from sleep.[1] OSA affects about 25% of adults in the USA and is a leading cause of excessive sleepiness, resulting in a lower quality of life, impaired work performance, and an increased risk of a car accident.[2]

OSA is also linked to various long-term health problems, including cardiovascular disease, metabolic disorders, and psychiatric problems.[3–5] Furthermore, numerous reports have associated cognitive difficulties in memory and new learning, attention, and executive function.[6–9] A meta-analysis of six prospective studies have found that 26% of patients with OSA experience significant cognitive decline or dementia.[10] Another study has found that the combined prevalence of depressive symptom in patients with OSA is about 35%.[11] Sleep fragmentation, often seen in patients with OSA, may play a role in the cognitive impairments associated with OSA by disrupting neural networks, particularly in the frontal lobes.[9] It contributes to cognitive impairments, particularly attention and memory problems.[12,13] Decreased sleep efficiency also reduces the efficacy of restorative processes, resulting in cellular and biochemical stress.[14,15] Another cause of cognitive impairments is the intermittent hypoxia associated with OSA.[16] These changes affect cell neurogenesis and the density in the hippocamus.[16,17] These factors contribute to OSA, increasing the risk of mild cognitive impairment, Alzheimer's disease (AD), and other types of dementia.[18–20]

Brain magnetic resonance imaging (MRI) studies have found that atrophy of the hippocampus and amygdala in older adults with normal cognitive function is a risk factor for developing dementia.[21] The amygdala's and hippocampus's asymmetric atrophy could also be a particularly sensitive indicator for detecting early cognitive impairments.[22] Previous research has found that patients with OSA have impaired attention, memory, emotion, and executive functions linked to multiple brain regions, especially in the amygdala and hippocampus.[23] The basolateral amygdala/hippocampus are the regions of structural atrophy and functional disturbances in OSA, and these changes are linked to emotional, sensory, and limbic dysfunction.[24] The limbic system is a network of interconnected cortical and subcortical structures that is responsible for connecting visceral states, emotion, and cognition to behavior.[25] It is well known that the limbic system's activation during sleep plays a crucial role in memory consolidation.[26] Thus, we could assume that the patients with OSA have abnormalities in the limbic system, which could be detected by brain MRI.

In the past, it was challenging to obtain volume automatically. Recently, machine learning techniques have become available to segment and determine the volumes of the limbic structures, including the hippocampus, amygdala, thalamus, mammary body, hypothalamus, basal forebrain, septal nuclei, fornix, and nucleus accumbens.[27] Furthermore, graph theory, which uses natural frameworks to handle large networks analytically, may quantify the topological configuration of brain connections and evaluate brain efficiency for information processing and network features.[28,29] Graph theory based on the limbic structure volumes can provide the state of the intrinsic limbic network. However, no studies have focused on limbic structure volumes and investigated the intrinsic limbic network in patients with OSA compared to healthy controls. Abnormalities in limbic structures in patients with OSA may suggest that OSA is associated with cognitive impairments.

We investigated the change in limbic structure volumes and intrinsic limbic network in patients with OSA in this study compared to healthy controls. We hypothesized that there were significant alterations of limbic structure volumes and intrinsic limbic networks in patients with OSA.

Methods

Participants: Patients with OSA and Healthy Controls

This study took place in a tertiary care hospital. The hospital's institutional review approved this study board, which was conducted in accordance with the Declaration of Helsinki. We retrospectively identified patients who met the following criteria for OSA: [30] 1) a diagnosis of OSA based on laboratory polysomnography demonstrating an apnea-hypopnea index (AHI) >5 in addition to symptoms such as sleepiness or chronic snoring, 2) OSA was the only medical or neurological disorder, 3) no structural lesions on brain MRI on visual inspection, 4) no complaints of cognitive impairment, and 5) with three-dimensional T1-weighted MRI data, which were suitable for volumetric analysis. Patients with OSA did not complain of memory loss or problems in daily living. We collected clinical and polysomnographic data from patients with OSA, including their age, sex, Epworth sleepiness scale score, total sleep time, sleep efficiency, the ratio of sleep stages N1, N2, N3, and R during sleep, total AHI during sleep, AHI during stage N, AHI during stage R, and total respiratory disturbance index during sleep.

We calculated a value of %AHI and defined the patients with non-rapid eye movement (NREM)-predominant OSA (more than 66.7% of %AHI) and rapid eye movement (REM)-predominant OSA (less than 33.3% of %AHI).[31]

Our control group was age and sex matched with study cases. They had been previously recruited from our study,[32] who did not have a history of medical or neurological disorders. They had a normal brain MRI on visual inspection. None complained of snoring or other OSA symptoms and, therefore, did not have polysomnography testing.

MRI Acquisition

All patients with OSA and controls underwent three-dimensional T1-weighted MRI on a 3 T MRI scanner with the following acquisition parameters: TI = 1300 ms, TR/TE = 8.6/3.96 ms, flip angle = 8°, and isotropic voxel size = 1 mm^3. To rule out structural lesions, they were scanned using standard brain MRI protocols, including FLAIR and T2-weighted imaging.

Calculation of Limbic Structure Volumes

The limbic structures were analyzed volumetrically using the development version of FreeSurfer program with the following steps. First, we used the FreeSurfer "recon-all" command[33] to process our three-dimensional T1-weighted MRI data. Using this command, we could obtain the volumes of the hippocampus, amygdala, and thalamus. Second, we used "mri_sclimbic_seg"[27] scripts to segment limbic structures and obtain their absolute volumes, including the mammary body, hypothalamus, basal forebrain, septal nuclei, fornix, and nucleus accumbens. This method used a U-net-based deep learning algorithm. All segmentations

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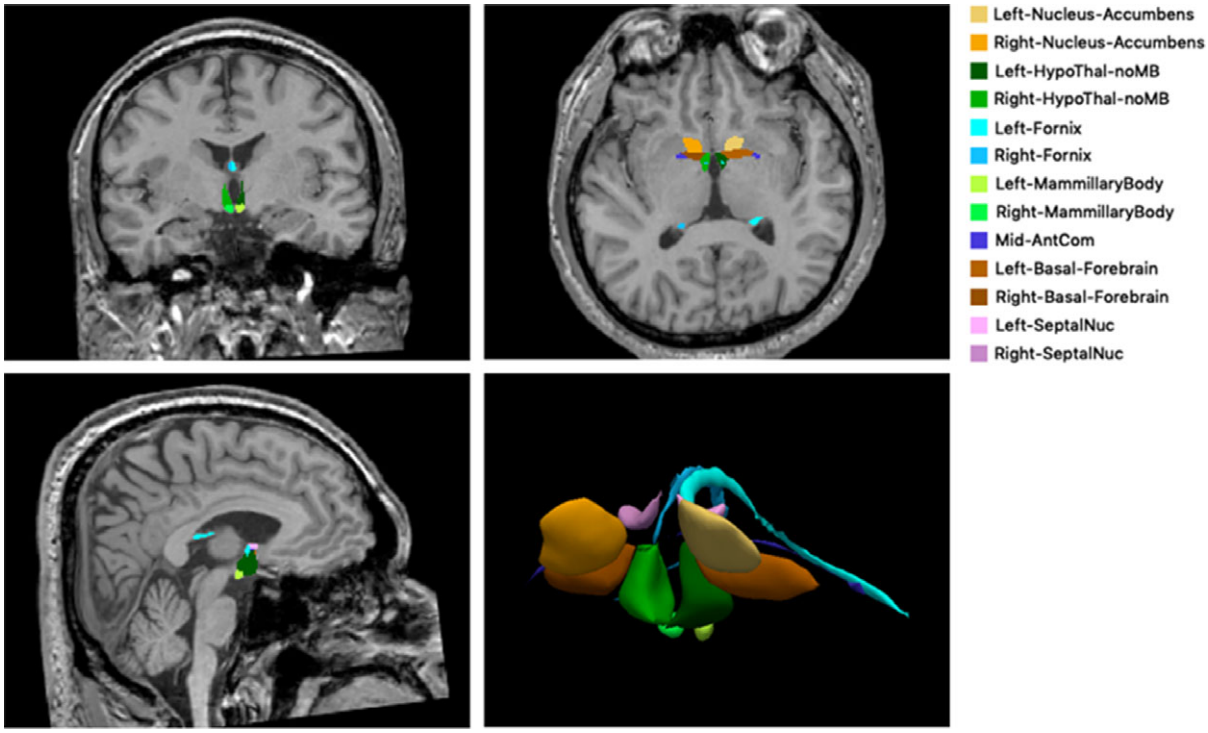

Figure 1: The example of segmentation of subcortical limbic structures. The segmentations are overlaid onto a T1-weighted image in coronal, axial, and sagittal orientation and shown in volume rendering. HypoThal-noMB: hypothalamus, AntCom: anterior commissure, SeptalNuc: septal nucleus.

were visually inspected for accuracy prior to inclusion in the group analysis to correct for a potential error in the automated procedure. Figure 1 illustrates an example of segmentation in limbic structures in a patient. Third, we corrected the limbic structure volumes for their estimated intracranial volumes.

Calculation of Intrinsic Limbic Network

We examined the intrinsic limbic network in patients with OSA and healthy controls using the Brain Analysis with Graph Theory (BRAPH) program.[34] This software develops a collection of nodes representing brain regions (individual volumes within limbic structures) and edges representing their connections (calculated as partial correlation coefficients between each pair of brain regions while controlling for age and sex effects) for each group. Each group was assigned a weighted, undirected connection matrix. We applied graph theory to determine the differences in the intrinsic limbic network between the groups using network measures such as average degree, average strength, radius, diameter, eccentricity, characteristic path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, assortativity, and small-worldness index.[35–37] These network parameters were compared between patients with OSA and healthy controls.

Statistical Analysis

The age and sex were compared using the chi-squared test and the Student's *t*-test, respectively, between the patients with OSA and healthy controls. We used Student's *t*-test to compare limbic structure volumes between the groups. We used nonparametric permutation tests with 1000 permutations to determine the statistical significance of the differences between the groups in the intrinsic limbic network, because we could obtain network measures at the group level through the BRAPH program data. We defined statistical significance as a *p*-value less than 0.05 for comparing baseline characteristics and correlations between the groups. All statistical analyses were carried out using MedCalc® Statistical Software, version 20.022 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Results

Clinical and Polysomnographic Characteristics

We enrolled 26 patients with OSA and 30 healthy controls. The groups did not differ by age and sex. Table 1 shows the clinical and polysomnographic characteristics of patients with OSA and healthy controls.

The Differences in Limbic Structure Volumes Between Patients with OSA and Healthy Controls

Table 2 reveals the differences in limbic structure volumes between patients with OSA and healthy controls. Significant differences existed between the groups' volumes of some limbic structures. The volumes in the right amygdala, right hippocampus, right hypothalamus, right nucleus accumbens, left amygdala, left basal forebrain, left hippocampus, left hypothalamus, and left nucleus accumbens in patients with OSA were lower than those in healthy controls.

The Differences in Limbic Structure Volumes Between Patients with NREM-Predominant OSA and REM-Predominant OSA

Eight patients were NREM-predominant OSA, whereas five patients were REM-predominant OSA. There were no significant differences in the limbic structures' volumes, including right and

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Table 1: The clinical and polysomnographic characteristics in the patients with obstructive sleep apnea

	Patients with obstructive sleep apnea (N = 26)	Patients with healthy controls (N = 30)	*p*-value
Clinical data			
Age ± SD, years	63.9 ± 9.6	63.9 ± 9.6	0.872
Male, N (%)	17 (65.3)	21 (70.0)	0.714
BMI, kg/m^2 (interquartile range)	24.2 (23.6–26)		
Epworth sleepiness scale (interquartile range)	6 (3-8)		
Polysomnographic data			
Total sleep time±SD, minutes	346.6 ± 54.8		
Sleep efficiency, % (interquartile range)	75 (71.9–82.9)		
Stage N1, % (interquartile range)	27.2 (12–34.3)		
Stage N2, % (interquartile range)	58.9 (46.7–66.1)		
Stage N3, % (interquartile range)	1.6 (0.5–4.8)		
Stage R, % (interquartile range)	15.1 (6.9–20.2)		
Total AHI (interquartile range)	15.4 (8.6–30.1)		
AHI during stage N (interquartile range)	15.8 (8.5–30.3)		
AHI during stage R (interquartile range)	12.4 (2.9–24.0)		
Total RDI (interquartile range)	17.7 (11.1–33)		

SD=standard deviation; BMI=body mass index; AHI=apnea-hypopnea index; RDI=respiratory disturbance index.

Table 2: The differences in limbic structure volumes between patients with OSA and healthy controls

	Patients with OSA (N = 26)		Healthy controls (N = 30)				
Structures	Mean (%)	SD (%)	Mean (%)	SD (%)	Difference (%)	95% CI	*p*-value
Right hemisphere							
Amygdala	0.102	0.013	0.113	0.014	0.011	0.0036 to 0.0184	* 0.004
Basal forebrain	0.021	0.003	0.023	0.004	0.002	−0.0002 to 0.0033	0.087
Fornix	0.031	0.005	0.032	0.006	0.001	−0.0020 to 0.0034	0.616
Hippocampus	0.253	0.026	0.281	0.036	0.028	0.0113 to 0.0455	* 0.002
Hypothalamus	0.028	0.003	0.032	0.004	0.003	0.0012 to 0.0052	* 0.002
Mammillary body	0.003	0.000	0.004	0.001	0.000	−0.0001 to 0.0004	0.240
Nucleus accumbens	0.021	0.005	0.024	0.005	0.003	0.0005 to 0.0055	* 0.019
Septal nuclei	0.007	0.001	0.007	0.001	0.000	−0.0002 to 0.0008	0.211
Thalamus	0.461	0.048	0.470	0.046	0.008	−0.0167 to 0.0337	0.503
Left hemisphere							
Amygdala	0.089	0.011	0.098	0.013	0.009	0.0026 to 0.0154	* 0.007
Basal Forebrain	0.020	0.003	0.022	0.003	0.002	0.0002 to 0.0034	* 0.027
Fornix	0.030	0.004	0.032	0.006	0.002	−0.0007 to 0.0052	0.138
Hippocampus	0.245	0.024	0.265	0.037	0.020	0.0031 to 0.0372	* 0.021
Hypothalamus	0.028	0.003	0.031	0.005	0.003	0.0005 to 0.0049	* 0.016
Mammillary body	0.003	0.000	0.003	0.001	0.000	−0.0002 to 0.0003	0.718
Nucleus accumbens	0.023	0.005	0.027	0.004	0.004	0.0014 to 0.0062	* 0.002
Septal nuclei	0.007	0.001	0.007	0.001	0.000	−0.0002 to 0.0009	0.268
Thalamus	0.503	0.062	0.505	0.059	0.001	−0.0311 to 0.0336	0.939

*$p < 0.05$.
OSA=obstructive sleep apnea.

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Table 3: The differences in the intrinsic limbic network between patients with OSA and healthy controls

Network measures	Patients with OSA (N = 26)	Healthy controls (N = 30)	Difference	CI lower	CI upper	*p*-value
Average degree	16.889	17.000	0.111	−1.553	1.942	0.476
Average strength	8.276	9.235	0.959	−5.662	5.447	0.539
Radius	3.277	2.086	−1.191	−2.706	2.701	0.512
Diameter	4.973	3.442	−1.531	−3.855	3.744	0.491
Eccentricity	3.824	2.959	−0.865	−3.224	3.159	0.524
Characteristics path length	2.221	1.956	−0.265	−1.490	1.514	0.513
Global efficiency	0.506	0.555	0.048	−0.287	0.265	0.520
Local efficiency	1.078	1.293	0.215	−1.250	1.132	0.538
Mean clustering coefficient	0.461	0.523	0.062	−0.347	0.347	0.525
Transitivity	0.694	0.785	0.091	−0.514	0.495	0.546
Modularity	0.032	0.029	−0.002	−0.099	0.095	0.512
Assortativity	−0.069	−0.059	0.010	−0.060	0.060	0.394
Small-worldness index	0.979	0.981	0.003	−0.085	0.094	0.446

OSA=obstructive sleep apnea; CI=95% confidence interval of difference.

left amygdala, basal forebrain, fornix, hippocampus, hypothalamus, mammary body, nucleus accumbens, septal nuclei, and thalamus between the groups (Suppl. 1).

The Differences in Intrinsic Limbic Network Between Patients with OSA and Healthy Controls

Table 3 shows the differences in the intrinsic limbic network between patients with OSA and healthy controls. There were no significant differences in network measures, including average degree, average strength, radius, diameter, eccentricity, characteristics path length, global efficiency, local efficiency, mean clustering coefficient, transitivity, modularity, assortativity, and small-worldness index, between the groups.

Correlation Between Clinical and Polysomnographic Characteristics and Limbic Structure Volumes

We conducted a correlation analysis between the limbic structure volumes, including the right amygdala, right hippocampus, right hypothalamus, right nucleus accumbens, left amygdala, left basal forebrain, left hippocampus, left hypothalamus, and left nucleus accumbens, and clinical and polysomnographic characteristics in patients with OSA. There was a significant negative correlation between volumes in the right amygdala, right nucleus accumbens, left amygdala, and left nucleus accumbens and age. However, there were no significant correlations between the limbic structure volumes, including the right hippocampus, right hypothalamus, left basal forebrain, left hippocampus, and left hypothalamus and the other clinical and polysomnographic characteristics (Table 4). Furthermore, we conducted a correlation analysis between the limbic structure volumes and age in the healthy controls, which showed no significant correlations between them (Suppl. 2.).

Discussion

We found differences between cases and controls in the limbic structure volumes of the right amygdala, right hippocampus, right hypothalamus, right nucleus accumbens, left amygdala, left basal forebrain, left hippocampus, left hypothalamus, and left nucleus accumbens using a U-net-based deep learning algorithm.[27] We also found no alterations of the intrinsic limbic networks in patients with OSA compared to healthy controls, which was analyzed based on the graph theory.

The volumes of the right amygdala, right hippocampus, right hypothalamus, right nucleus accumbens, left amygdala, left basal forebrain, left hippocampus, left hypothalamus, and left nucleus accumbens were significantly lower in patients with OSA than in the controls. This finding was consistent with a previous meta-analysis, which showed structural atrophy in the basolateral amygdala, hippocampus, and insular cortex in patients with OSA.[24] These findings suggest the important role of the amygdala, hippocampus, and insula in abnormal emotional and sensory processing in patients with OSA. The right amygdala is thought to mediate aversive conditioning to errors, while the left amygdala is believed to underpin negative performance affect.[38] Synaptic plasticity in the basolateral amygdala is shown to mediate the acquisition of associative memories of both ends of emotional valences, and different populations of neurons in that complex may encode fearful or rewarding associations.[39] In major depressive disorder, abnormal functional connectivity of the amygdala and hippocampus may interact with dysfunctional intrinsic network activity, which could underlie emotional memory disturbances in patients with OSA.[40] Thus, the findings with a decrease in amygdala volume in patients with OSA may suggest that this role of amygdala may have declined in patients with OSA.[41]

Furthermore, the hippocampus is particularly vulnerable to intermittent hypoxia, which could explain the high frequency of neurobehavioral deficits in patients with OSA.[42] A recent study discovered a link between OSA and AD. Cognitive impairments observed in patients with OSA could be partly explained by hippocampal dysfunction, as previously demonstrated in patients with AD.[43] In addition, another study discovered that patients with AD were five times more likely than healthy controls to develop OSA symptoms.[19] The right hippocampus is known to be involved in memory tasks that require concentric spatial location

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Table 4: The results of correlation analysis between clinical and polysomnographic characteristics and limbic structures volumes in the patients with obstructive sleep apnea

		Right amygdala	Right hippocampus	Right hypothalamus	Right nucleus accumbens	Left amygdala	Left Basal forebrain	Left hippocampus	Left Hypothalamus	Left Nucleus accumbens
Age	Correlation coefficient	−0.435	−0.323	−0.153	−0.535	−0.425	−0.290	−0.153	−0.183	−0.428
	p-value	* 0.027	0.108	0.457	* 0.005	* 0.030	0.151	0.454	0.372	* 0.029
BMI	Correlation coefficient	−0.059	0.007	0.007	−0.204	−0.211	0.144	−0.028	0.060	−0.232
	p-value	0.773	0.975	0.972	0.318	0.301	0.483	0.894	0.773	0.254
Epworth sleepiness scale	Correlation coefficient	−0.071	−0.214	−0.347	−0.029	−0.062	−0.343	−0.271	−0.269	−0.167
	p-value	0.729	0.294	0.082	0.888	0.763	0.086	0.181	0.183	0.416
Total sleep time	Correlation coefficient	0.172	0.297	0.214	−0.029	0.234	0.168	0.201	0.339	0.061
	p-value	0.400	0.141	0.295	0.888	0.249	0.411	0.325	0.090	0.767
Sleep efficiency	Correlation coefficient	0.081	0.106	−0.107	−0.084	−0.007	0.054	0.004	−0.020	−0.050
	p-value	0.696	0.607	0.602	0.685	0.972	0.795	0.984	0.922	0.808
Total AHI	Correlation coefficient	−0.037	−0.123	−0.094	−0.219	−0.134	0.069	0.016	−0.119	−0.218
	p-value	0.859	0.551	0.647	0.284	0.513	0.739	0.938	0.561	0.285
AHI during stage N	Correlation coefficient	−0.021	−0.114	−0.142	−0.183	−0.131	0.031	−0.021	−0.176	−0.210
	p-value	0.920	0.580	0.488	0.372	0.522	0.882	0.917	0.390	0.303
AHI during stage R	Correlation coefficient	−0.027	0.139	0.057	−0.286	−0.136	0.109	0.069	0.072	−0.273
	p-value	0.897	0.499	0.782	0.157	0.507	0.595	0.736	0.727	0.177
Total RDI	Correlation coefficient	−0.061	−0.147	−0.128	−0.262	−0.168	0.033	0.014	−0.177	−0.258
	p-value	0.767	0.473	0.532	0.195	0.413	0.872	0.947	0.386	0.204
Sleep stage N1	Correlation coefficient	0.126	−0.277	−0.399	0.054	−0.122	0.047	−0.261	−0.345	−0.077
	p-value	0.538	0.171	* 0.043	0.795	0.552	0.819	0.197	0.084	0.709

*$p < 0.05$.
BMI=body mass index; AHI=apnea-hypopnea index; RDI=respiratory disturbance index.

processing, which could impair driving ability in patients with OSA.[44] This is in a line with the finding of the present study showing the significant difference in hippocampus volume between patients with OSA and healthy controls.

The nucleus accumbens is one forebrain nuclei that play a crucial role in pain modulation and sleep-wake cycle regulation.[45] Dopaminergic activity at the inhibitory D2 receptor reduces nucleus accumbens output, increases arousal, and disrupts sleep status.[46] The nucleus accumbens is more activated during forced wakening than during uninterrupted sleep, according to a study on forced wakening by time division.[47] In this study, the nucleus accumbens volume in patients with OSA was lower than that in the healthy controls, which may be related to poor sleep quality in OSA. Changes in the nucleus accumbens caused by forced awakening may be linked to sleep fragmentation, affecting cognitive impairments in patients with OSA. These findings suggested that changes in the limbic structure volumes in patients with OSA are related to developing cognitive impairments.

However, our study revealed no differences in the intrinsic limbic network between patients with OSA and a healthy control group. The present results differed from previous studies that analyzed the entire brain network. In one study, researchers investigated structural brain connectivity using diffusion tensor imaging and discovered that white matter abnormalities in patients with OSA caused changes in structural connectivity.[48] Another study found that OSA caused changes in global topological characteristics in the brain network, demonstrated by statistical cortical volume associations.[49] There are several reasons for different results. A plausible explanation is that the intrinsic limbic network is likely to differ from the global brain network, which we did not analyze. Another possibility is that our small sample size had insufficient power to detect a difference. Further research with larger sample sizes is needed to confirm our findings.

There were some limitations in this study. First, this study was limited to a single center and relatively small sample size, limiting generalizability. Second, a temporal relationship could not be determined because this was a retrospective study comparing patients with OSA and healthy controls. As a result, it was unclear whether the change in limbic structure volumes was the result or cause of OSA. Third, we included the control group without polysomnographic examination and may have included individuals with undiagnosed sleep apnea. Lastly, since limbic structures were very small, it was difficult to completely rule out the possibility of errors in segmentation. However, we used the toolbox based on the U-Net for segmentation of limbic structures, which was one of the recent machine learning algorithms. It had been trained using 39 manually labeled MRI data sets for spatial, intensity, contrast, and noise augmentation. Test–retest reliability of the tool was already proven.[27] Nevertheless, this was the first study to focus on changes in limbic structural volumes and intrinsic limbic networks based on the graph theory in patients with OSA compared to healthy controls. Significant volume changes in the several limbic structures were successfully confirmed.

Conclusion

We demonstrate that the volumes of several limbic structures in patients with OSA are significantly lower than those in healthy controls. However, there are no alterations to the intrinsic limbic network. These findings suggest that OSA is one of the risk factors for cognitive impairments.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/cjn.2022.303

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