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Decreased Memory-related Regional Cerebral Perfusion in Severe Obstructive Sleep Apnoea With a Mild Cognitive Impairment

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Abstract

We will use arterial spin labeling (ASL) technology to quantify and evaluate abnormal changes in resting state cerebral blood perfusion in patients with obstructive sleep apnea (OSA) with cognitive impairment (CI) and to explore the underlying neuropathological mechanisms in patients with OSA and CI (OSA-CI).
The findings are basically in line with our study hypothesis.OSA-CI patients, similar to AD and MCI, may initially present with decreased memory function. The progressive aggravation of hemodynamic abnormalities in the bilateral inferior temporal gyrus and left lingual gyrus in OSA patients may contribute to decreased brain memory function and subsequent memory dysfunction.

Materials

All the neuropsychological tests involved in the study are included in the following documents.

Appendix.doc 147KB

Troubleshooting

1

Research objectives

2 We will use arterial spin labeling (ASL) technology to quantify and evaluate abnormal changes in resting state cerebral blood perfusion in patients with obstructive sleep apnea (OSA) with cognitive impairment (CI) and to explore the underlying neuropathological mechanisms in patients with OSA and CI (OSA-CI). Additionally, we will investigate whether the decline in memory function was more pronounced compared to other cognitive function types. Furthermore, we will examine the progression of blood perfusion abnormalities from good sleepers (GS) to confirmed OSA patients and finally to those with mild cognitive impairment.

Research Background

3 Obstructive sleep apnea (OSA) is characterized by recurrent upper airway collapse and obstruction during sleep, leading to obstructive apnea, hypopnea, or breathing-related arousal[-]. OSA can result in intermittent hypoxemia, sleep fragmentation, repeated awakenings, and hypercapnia, contributing to daytime sleepiness and an increased risk of traffic accidents. Moreover, OSA is associated with cognitive impairment (OSA-CI)[5], diabetes, and Alzheimer's disease. Specifically, OSA-CI patients may experience deficits in attention, memory, executive function, emotion regulation, visuospatial abilities, fine coordination, and language skills. However, the neuropathological basis underlying the development of cognitive impairment in OSA patients remains unclear. Therefore, investigating the neuroimaging mechanisms associated with cognitive function in OSA is crucial for early clinical prevention and diagnosis of OSA-CI.
Although the brain regions with abnormal blood perfusion in OSA patients differ from those in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), OSA-CI may manifest initially with decreased memory function, similar to MCI and early AD[-]. From the perspective of cerebral blood perfusion, decreased cerebral blood perfusion in OSA patients occurs in brain areas related to memory function (e.g., bilateral parahippocampal gyrus and left lingual gyrus)[22,]. From the perspective of disease comorbidity, OSA is known to contribute to neurological diseases such as MCI and AD with early memory loss[5,8]. From the perspective of the structure and characteristics of human blood vessels, temporal brain regions like the inferior temporal gyrus and the parahippocampal gyrus are relatively distant from the main blood vessels, resulting in normal blood oxygen content in these regions only suffice for basic neural activity maintenance[24]. Furthermore, the temporal hippocampal gyrus has less vascular expansion capacity compared to other brain regions, making it more easily or earlier to

suffer from insufficient blood supply and oxygen deprivation, potentially leading to a decline in memory function[24]. Thus, once brain blood perfusion becomes abnormal, it may initially impact blood supply to distal brain regions (such as the hippocampal gyrus), consequently affecting memory function, which aligns with the observation that AD typically manifests with memory loss first[24]. Based on these perspectives, we hypothesized that during progression from no cognitive impairment to mild cognitive impairment, memory function in severe OSA deteriorates more significantly than other cognitive functions, and more abnormal perfusion brain regions are associated with memory function.

Considering that patients with OSA need to undergo prolonged abnormal perfusion of cerebral blood to develop cognitive impairment, and previous studies found only abnormal brain perfusion in patients with severe OSA[25], we divided participants into three groups: good sleepers (GS), severe OSA no cognitive impairment (OSA-NCI), and severe OSA with cognitive impairment (OSA-CI). This helps us to explore the neuropathological mechanism of OSA-CI, but also helps us to analyze the cerebral blood perfusion dynamic development process of OSA disease from healthy state to confirmed OSA to producing mild cognitive impairment. Based on the idea that prolonged abnormal cerebral blood perfusion affects brain function, we hypothesized that blood perfusion in memory-related brain regions decreases sequentially in three groups (GS < OSA-NCI < OSA-CI).

Some neuroimaging studies have found that factors such as age, sex, body mass index (BMI), drowsiness level, and global mean brain blood perfusion can cause differences in blood perfusion in local brain regions[11]. Therefore, when examining group differences in blood perfusion in local brain areas, it is essential to control for these factors to ensure comparability between the groups.

Compared with the GS group, the OSA group exhibited increased blood perfusion in certain brain regions, attributed to a temporary compensatory increase in blood perfusion due to disrupted normal cerebral blood perfusion balance[22]. Additionally, given that more severe OSA was associated with higher BMI and sleepiness levels, differences in BMI and sleepiness levels between the GS groups and severe OSA group were possible, which also meant that it was difficult to control for differences in BMI and sleepiness levels between the GS group and OSA group. However, the group differences in BMI and sleepiness levels between the OSA-NCI and OSA-CI groups were easily counterbalanced out. Therefore, directly comparing differences in regional brain blood perfusion between the OSA-NCI group and OSA-CI group in the present study may help mitigate the influence of BMI, drowsiness levels, and compensatory mechanisms in brain blood supply.

We quantified and evaluated the abnormal changes in resting-state brain blood perfusion in OSA-CI using ASL, and analyzed the correlation between abnormal brain blood perfusion volume and cognitive function scores, aiming to explore the underlying neuropathological mechanisms of OSA-CI. Additionally, we investigated whether the decline in memory function was more pronounced compared to other cognitive function

types and incidentally analyzed the dynamic development of blood perfusion in OSA disease from a healthy state to confirmed OSA and subsequently to mild cognitive impairment.

Research Plan and Method

4 Research Plan and Method

4.1 **Participants:**Participants will be divided into two groups: 15-20 good sleepers (GS: AHI < 5 events/hour; MoCA score ≥ 26 points) and 30-40 untreated OSA patients diagnosed by polysomnography (PSG). All participants will complete the Montreal Cognitive Assessment (MoCA). The OSA patients will be further categorized into two groups based on their cognitive status: OSA-CI patients (AHI ≥ 5 events/hour; MoCA score < 26 points) and OSA-NCI patients (AHI ≥ 5 events/hour; MoCA score ≥ 26 points).
All participants in this study were had at least 9 years of education, and were right-handed. None had severe respiratory diseases, central or mixed apnea as confirmed by PSG. Additionally, all participants were free from alcohol or illicit drug use, and were not taking psychoactive drugs. Moreover, none had intracranial structural lesions such as severe white matter lesions, cerebrovascular disease lesions, brain atrophy, brain trauma, cerebral infarction, cerebral hemorrhage, or brain tumors.

4.2 **Polysomnographic Assessment:**The overnight polysomnography examinations will be conducted in the sleep monitoring room of the Otolaryngology Department at Zhongshan Hospital of Dalian University. On the monitoring day, subjects will refrain from napping and consuming alcohol, coffee, sedatives, hypnotics, and similar substances. The Philips Alice 6 system will be utilized to record oral and nasal airflow, chest and abdominal movements, finger oxygen saturation, snoring, EEG, electrooculography, electrocardiogram, and electromyography over a 7-hour period at night. Subsequently, sleep-related parameters such as apnea-hypopnea index (AHI, events/h), minimum oxygen saturation (Minimal SaO_2,%), oxygen desaturation index (events/h), and micro-arousal index (events/h) will be obtained. OSA severity will be classified as light, moderate, or severe according to the 2012 American Academy of Sleep Medicine (AASM) guidelines: mild (5 < AHI < 15 events/hour), moderate (15 ≤ AHI < 30 events/hour), and severe (AHI ≥ 30 events/hour).

4.3 **Neuropsychological scales:**All neuropsychological scales will be administered prior to the MRI scan. Each participant will complete the following scales sequentially:
The Montreal Cognitive Assessment (MoCA) is a widely used scale for screening cognitive dysfunction, encompassing executive function, immediate recall, word fluency, orientation, calculation, abstraction, delayed recall, visual perception, and nomenclature. Scores range from 0 to 30, with a score of 26 or higher considered normal, and less than 26 indicating cognitive impairment.

The Epworth Sleepiness Scale (ESS) comprises eight self-rated questions, with a total score of 24. A score of 6 indicates sleepiness, 11 indicates excessive sleepiness, and 16 indicates severe sleepiness.
The Self-Rating Anxiety Scale (SAS) consists of 20 self-rating questions, graded on a scale of 4, with a total score range of 20 to 80. The anxiety index is calculated as (total score × 1.25). A score of below 50 indicates normal anxiety, 50 to 59 indicates mild anxiety, 60 to 69 indicates moderate anxiety, and above 70 indicates severe anxiety.
The Self-Rating Depression Scale (SDS) also comprises 20 self-rating questions, with a total score range of 20 to 80. The depression index is calculated as (total score/80). A depression index of less than 0.5 indicates normal depression, 0.5 to 0.59 indicates mild depression, 0.6 to 0.69 indicates moderate depression, and greater than 0.7 indicates major depression.

4.4 **MRI Data Acquisition:**All participants will undergo imaging using a Siemens 3.0T Magnetom Verio system equipped with a 12-channel head coil. The scanned sequences include3D-T1-weighted imaging (3D-T1WI) and PASL. Participants will be positioned supine on the examination bed and wore noise-canceling headphones. Sponge foam will be used to secure the sides of their head. Participants will be instructed to maintain body stability and keep their brain awake during the scan.
A 3D-T1WI sequence will be employed, with parameters including TR of 1900 ms, TE of 2.79 ms, 176 slices with a slice thickness of 1 mm, voxel size of 0.7 mm × 0.7 mm × 1.0 mm, matrix size of 384 × 384, FOV of 259 mm × 259 mm, and FA of 9°. The scan duration was 6 minutes and 27 seconds. Additionally, PASL imaging will be utilized, with parameters including TR of 2500 ms, TE of 11 ms, FA of 90°, bandwidth of 2790 Hz/pixel, label-delay of 1800 ms, FOV of 230 mm × 230 mm, and slice thickness of 6 mm. These sequences will be used to gather structural brain information for further analysis.

4.5 **Image Preprocessing:**First, two senior imaging diagnosticians will review the T2-FLAIR and T1WI images of each subject, identifying and excluding those with poor image quality (due to false artifacts and incomplete images) and parenchymal lesions. Image preprocessing of cerebral blood flow perfusion images will be performed using the ASLtbx toolkit (available at https://www.cfn.upenn.edu/ASLtbx.php) on the MATLAB 2013b platform. The specific steps are as follows: 1) Format conversion: The original DICOM images will be converted into NIFTI format images. 2) Spatial standardization: The registered structural images will be spatially standardized based on the MNI template. The deformation field generated from this process will be applied to the cerebral blood flow perfusion map, resulting in the spatially standardized cerebral blood flow perfusion map. 3) Registration: The linear transformation of the T1-weighted anatomical structure image will be registered to the cerebral blood flow perfusion image. 4) Obtain rCBF map: ASLtbx will be used to process the spatial standardized images, obtaining the whole-brain average rCBF map. 5) Normalization: The average rCBF map will be normalized, meaning the rCBF value of each voxel was divided by the whole-brain mean. 6) Smoothing: A 6-mm Gaussian smoothing kernel will be applied to smooth the normalized images, preparing them for subsequent statistical analysis.

Statistical Analysis

5 Statistical analysis of demographic data, neuropsychological scale scores, and PSG parameters in the CI, NCI, and GS groups will be conducted using IBM SPSS Statistics 20.0 software. Initially, we will employ one-way ANOVA to analyze the three groups, followed by multiple comparisons between pairs of groups using the least significant difference test (LSD-t). Sex comparison among the participants in the three groups will be assessed using the chi-square test.
For the analysis of rCBF values, voxel-level one-way ANOVA will be performed for the three groups using SPM software. Sex, age, years of education, BMI values, and whole-brain gray matter mean CBF values will be included as covariates. Brain regions exhibiting statistically significant differences in rCBF values among the three groups will be identified as regions of interest (ROI). The DPABI software extracte the rCBF values for each ROI for all participants. Post hoc tests entailed pairwise comparison of rCBF values among the three groups using independent sample t-tests, with results subjected to false discovery rate (FDR) correction (cluster > 50 voxels).
Pearson correlation analysis will be conducted using IBM SPSS Statistics 20.0 software to examine the relationship between the rCBF value in statistically different brain regions between the CI and NCI groups and the scores of each MoCA item (including visual space and executive function, attention, language, abstraction, delayed memory, orientation, and naming scores).

Reference

6 1 Bixler E O, Vgontzas A N, Ten Have T, et al. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med*. 1998; 157(1): 144-8. doi:10.1164/ajrccm.157.1.9706079
2 Bixler E O, Vgontzas A N, Lin H M, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med*. 2000; 160(15): 2289-95. doi:10.1001/archinte.160.15.2289
3 Lim D C, Pack A I. Obstructive sleep apnea and cognitive impairment: addressing the blood-brain barrier. *Sleep Med Rev*. 2014; 18(1): 35-48. doi: 10.1016/j.smrv.2012.12.003
4 Ferri R, Drago V, Arico D, et al. The effects of experimental sleep fragmentation on cognitive processing. *Sleep Med*. 2010; 11(4): 378-85. doi: 10.1016/j.sleep.2010.01.006
5 Punjabi N M. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008; 5(2): 136-43. doi: 10.1513/pats.200709-155MG
6 Senaratna C V, Perret J L, Lodge C J, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev*. 2017; 34: 70-81. doi: 10.1016/j.smrv.2016.07.002
7 Floras J S. Hypertension and Sleep Apnea. *Can J Cardiol*. 2015; 31(7): 889-97. doi: 10.1016/j.cjca.2015.05.003

8 Reutrakul S, Mokhlesi B. Obstructive Sleep Apnea and Diabetes: A State of the Art 7 Review. *Chest*. 2017; 152(5): 1070-1086. doi: 10.1016/j.chest.2017.05.009
9 Bucks R S, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology*. 2013; 18(1): 61-70. doi: 10.1111/j.1440-1843.2012.02255.x
10 Petersen R C, Lopez O, Armstrong M J, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90(3): 126-135. doi: 10.1212/WNL.0000000000004826
11 Shaw, K., Bell, L., Boyd, K. *et al.* Neurovascular coupling and oxygenation are decreased in hippocampus compared to neocortex because of microvascular differences. *Nat Commun*. 2021; 12(1): 3190. doi: 10.1038/s41467-021-23508-y
12 Innes C R, Kelly P T, Hlavac M, et al. Decreased Regional Cerebral Perfusion in Moderate-Severe Obstructive Sleep Apnoea during Wakefulness. *Sleep*. 2015; 38(5): 699-706. doi: 10.5665/sleep.4658
13 Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep.* 1991; 14:486–95. doi: 10.1093/sleep/14.6.486
14 Chen JJ, Rosas HD, Salat DH. Age-associated reductions in cerebral blood flow are independent from regional atrophy. *NeuroImage*. 2011;55:468–78. doi: 10.1016/j.neuroimage.2010.12.032
15 Liu Y, Zhu X, Feinberg D, et al. Arterial spin labeling MRI study of age and gender effects on brain perfusion hemodynamics. *Magn Reson Med.* 2012;68:912–22. doi: 10.1002/mrm.23286
16 Poudel GR, Innes CRH, Jones RD. Cerebral perfusion differences between drowsy and non-drowsy individuals following acute sleep restriction. *Sleep*. 2012; 35:1085–96. doi: 10.5665/sleep.1994
17 Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry*. 2007; 52(5): 329-32. doi: 10.1177/070674370705200508
18 Chung K F. Use of the Epworth Sleepiness Scale in Chinese patients with obstructive sleep apnea and normal hospital employees. *J Psychosom Res*. 2000; 49(5): 367-72. doi: 10.1016/S0022-3999(00)00186-0
19 Samakouri M, Bouhos G, Kadoglou M, et al. Standardization of the Greek version of Zung's Self-rating Anxiety Scale (SAS). *Psychiatriki*. 2012; 23(3): 212-20. PMID: 23073544
20 Zung W W, Richards C B, Short M J. Self-rating depression scale in an outpatient clinic. Further validation of the SDS. *Arch Gen Psychiatry*. 1965; 13(6): 508-15. doi: 10.1001/archpsyc.1965.01730060026004

Protocol references

1 Bixler E O, Vgontzas A N, Ten Have T, et al. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am J Respir Crit Care Med*. 1998; 157(1): 144-8. doi:10.1164/ajrccm.157.1.9706079

2 Bixler E O, Vgontzas A N, Lin H M, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med*. 2000; 160(15): 2289-95. doi:10.1001/archinte.160.15.2289

3 Lim D C, Pack A I. Obstructive sleep apnea and cognitive impairment: addressing the blood-brain barrier. *Sleep Med Rev*. 2014; 18(1): 35-48. doi: 10.1016/j.smrv.2012.12.003

4 Ferri R, Drago V, Arico D, et al. The effects of experimental sleep fragmentation on cognitive processing. *Sleep Med*. 2010; 11(4): 378-85. doi: 10.1016/j.sleep.2010.01.006

5 Punjabi N M. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008; 5(2): 136-43. doi: 10.1513/pats.200709-155MG

6 Senaratna C V, Perret J L, Lodge C J, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev*. 2017; 34: 70-81. doi: 10.1016/j.smrv.2016.07.002

7 Floras J S. Hypertension and Sleep Apnea. *Can J Cardiol*. 2015; 31(7): 889-97. doi: 10.1016/j.cjca.2015.05.003

8 Reutrakul S, Mokhlesi B. Obstructive Sleep Apnea and Diabetes: A State of the Art 7 Review. *Chest*. 2017; 152(5): 1070-1086. doi: 10.1016/j.chest.2017.05.009

9 Bucks R S, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology*. 2013; 18(1): 61-70. doi: 10.1111/j.1440-1843.2012.02255.x

10 Petersen R C, Lopez O, Armstrong M J, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90(3): 126-135. doi: 10.1212/WNL.0000000000004826

11 Shaw, K., Bell, L., Boyd, K. *et al.* Neurovascular coupling and oxygenation are decreased in hippocampus compared to neocortex because of microvascular differences. *Nat Commun*. 2021; 12(1): 3190. doi: 10.1038/s41467-021-23508-y

12 Innes C R, Kelly P T, Hlavac M, et al. Decreased Regional Cerebral Perfusion in Moderate-Severe Obstructive Sleep Apnoea during Wakefulness. *Sleep*. 2015; 38(5): 699-706. doi: 10.5665/sleep.4658

13 Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep.* 1991; 14:486–95. doi: 10.1093/sleep/14.6.486

14 Chen JJ, Rosas HD, Salat DH. Age-associated reductions in cerebral blood flow are independent from regional atrophy. *NeuroImage*. 2011;55:468–78. doi: 10.1016/j.neuroimage.2010.12.032

15 Liu Y, Zhu X, Feinberg D, et al. Arterial spin labeling MRI study of age and gender effects on brain perfusion hemodynamics. *Magn Reson Med.* 2012;68:912–22. doi: 10.1002/mrm.23286

16 Poudel GR, Innes CRH, Jones RD. Cerebral perfusion differences between drowsy and non-drowsy individuals following acute sleep restriction. *Sleep*. 2012; 35:1085–96. doi: 10.5665/sleep.1994

17 Smith T, Gildeh N, Holmes C. The Montreal Cognitive Assessment: validity and utility in a memory clinic setting. *Can J Psychiatry*. 2007; 52(5): 329-32. doi: 10.1177/070674370705200508

18 Chung K F. Use of the Epworth Sleepiness Scale in Chinese patients with obstructive sleep apnea and normal hospital employees. *J Psychosom Res*. 2000; 49(5): 367-72. doi: 10.1016/S0022-3999(00)00186-0

19 Samakouri M, Bouhos G, Kadoglou M, et al. Standardization of the Greek version of Zung's Self-rating Anxiety Scale (SAS). *Psychiatriki*. 2012; 23(3): 212-20. PMID: 23073544

20 Zung W W, Richards C B, Short M J. Self-rating depression scale in an outpatient clinic. Further validation of the SDS. *Arch Gen Psychiatry*. 1965; 13(6): 508-15. doi: 10.1001/archpsyc.1965.01730060026004