# Correlation Study of Cognitive Function and Brain Spectral Metabolism, White Matter Hyperintensity in Patients with OSAHS

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**Abstract:** Sleep is an essential physiological process in human life. When people sleep, numerous cellular reactions occur, develop, and interact. These reactions facilitate bodily repair and regeneration,providing better mental and physical support for the following day. Despite its importance, sleep problems are widespread throughout the population. According to the International Classification of Sleep Disorders, 3rd Edition (ICSD-3), released in 2014, sleep disorders are categorized into several types. These include Sleep-related breathing disorders, Central disorders of hypersomnolence, Circadian rhythm sleep-wake disorders, Insomnia, Parasomnias and Sleep-related movement disorders.

***Keywords*:** obstructive sleep apnea hypopnea syndrome; cognitive function; hydrogen proton magnetic resonance spectroscopy; white matter high signa

## 1. Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a prevalent sleep disorder affecting 15% to 24% of adults [1]. It is characterized by repeated episodes of apnea and hypopnea during sleep. Clinically, it manifests as snoring, loud and irregular snoring, sensations of suffocation or nocturnal awakenings, sleep disturbances, and memory decline. In severe cases, cognitive impairment and behavioral abnormalities may occur. The initial clinical symptoms of OSAHS are often subtle and may persist for several years before patients seek medical attention. Patients may report intermittent nocturnal awakenings, insomnia, reduced total sleep time, and fragmented sleep [2]. OSAHS is defined as the recurrence of apnea and hypopnea more than 30 times during nighttime sleep or an Apnea-Hypopnea Index (AHI)≥5 events per hour [3]. The pathophysiological mechanisms of OSAHS include complete or partial airway obstruction due to pharyngeal collapse during sleep, leading to the disappearance (apnea) or reduction of inspiratory airflow, decreased oxygen saturation, micro-arousals, hypopnea, and disruption of sleep architecture [4]. Libby et al.[5]demonstrated that nocturnal intermittent hypoxia (IH) in OSAHS patients can elevate the risk of atherosclerosis by inducing systemic inflammatory responses, thereby contributing to the onset and progression of cardiovascular and cerebrovascular diseases. Recent evidence increasingly highlights the significant association between OSAHS and conditions such as heart failure, arrhythmia, hypertension, coronary artery disease, stroke, and cognitive dysfunction [6].

## 2. Cognitive function

Cognitive function is composed of multiple cognitive domains, including memory, calculation, visuospatial orientation, attention, executive function, language understanding and expression application, etc.[7] Cognitive dysfunction refers to the impairment of cognitive function to varying degrees caused by different factors. Clinically, it can be manifested as difficulty concentrating, memory decline, decreased executive function, and reduced reasoning and abstract thinking abilities, etc. [8] The cognitive impairment of patients with OSAHS can be systematically evaluated through neuropsychological scales, electrophysiological indicators and neuroimaging features. Common Cognitive function Assessment scales include the Montreal Cognitive Assessment (MoCA) and the Mini-Mental Status Exam (MMSE), etc. The evaluations of both the MMSE scale and the MoCA scale are subjective. Therefore, in our study, E-prime software was used to measure cognitive function, ANT was used to assess the attention network, and SCWT was used to test executive function. Posner et al. [9] proposed that ANT can be divided into three parts: the alertness network, the orientation network, and the executive control network. Each part has its specific neuroanatomical and biochemical mechanisms. The alertness network is mainly to generate and maintain the best alertness to detect upcoming stimuli. Directional networks select high-priority information from numerous sensory inputs for further processing. The execution control network is to resolve the conflicts among numerous stimuli. It can reflect the selective impairment of specific attention subdomains. According to pharmacological, electrophysiological and neuroimaging studies, these attention subdomains involve different anatomical regions of the brain

[10-11]. The alertness network is related to the thalamic and parietal cortex networks in the right hemisphere. The orientation network is related to the temporoparietal junction and the parietal lobe. The executive control network is related to the midline frontal lobe area and the prefrontal cortex, and also has connections with the anterior cingulate gyrus, the lateral prefrontal cortex and the right inferior frontal gyrus [12]. Beebe and Gozal confirmed that executive dysfunction in OSAHS is mainly involved in the frontal cortex [13-14].

## 3. Cognitive dysfunction related to OSAHS

More and more studies have found that OSAHS is a serious sleep breathing disorder, mainly characterized by recurrent airway stenosis and obstruction during sleep and IH. IH damages extensive cognitive functional areas such as the cerebral cortex and hippocampus, leading to functional impairments such as memory, attention, executive ability, computational ability, and visuospatial functions[15-16]. Sleep fragmentation related to OSAHS is closely associated with persistent attention disorders and daytime sleepiness in patients [17]. Some studies suggest that IH in patients with OSAHS is correlated with executive function and attention disorders. OSAHS can affect the prefrontal cortex by inducing cellular structure damage through IH [18]. Sleep fragmentation of OSAHS can disrupt the circadian rhythm of cortisol by activating the hypothalamic-pituitary-adrenal axis, further leading to degeneration of the prefrontal cortex, an increase in the number of awakenings, and a decline in short-term memory. It is a strong predictor of memory impairment [19]; Circadian rhythm disorders cause changes in the cortisol levels and cytokine levels of patients, resulting in reduced learning and memory in patients [20]. However, the underlying mechanism by which OSAHS leads to cognitive dysfunction remains unclear. Recurrent IH at night can activate hypoxia-inducible factor-1 α, promote excessive generation of reactive oxygen species, trigger oxidative stress responses, directly damage frontal cortical neurons, and lead to synaptic plasticity and abnormal metabolism of neurotransmitters (such as acetylcholine). IH significantly increases the generation level of reactive oxygen species by activating the NADPH oxidase pathway, thereby inducing abnormal secretion of vasoactive mediators, including elevated endothelin-1 and decreased bioavailability of nitric oxide. This oxidative stress cascade reaction can directly damage vascular endothelial cells and cause endothelial dysfunction [21]. IH can cause vasoconstriction and an increase in red blood cells, resulting in a slower blood flow velocity, aggravating ischemia and hypoxia in brain tissue, and causing extensive damage to brain cells [22].

## 4. White matter hyperintensities (WMH)

On MRI images, WMH mainly presents as multiple punctate, patchy and fused abnormal signals around the bilateral lateral ventricles or in the subcortical white matter. It shows high signal on T2WI and FLAIR, and low signal on T1WI [23]. WMH is regarded as one of the imaging markers of cerebral small vessel disease [24]. The prevalence of WMH increases significantly with age. Among people over 40 years old, 50% have WMH, and the incidence of WMH in people aged 60 and above can be as high as 95%[25]. The risk factors of WMH include age, hypertension, diabetes, smoking, obesity and genetic factors, etc.[26-27]. The pathogenesis of WMH may be related to hypoxia-hypoperfusion: Due to the lack of collateral circulation in the white matter area of the brain, it is vulnerable to blood pressure fluctuations. Long-term hypoperfusion (cerebral blood flow < 35 mL/100g/min) can induce mitochondrial dysfunction of oligodendrocytes, resulting in reduced myelin synthesis and impaired axonal transport. Blood-brain barrier disruption: The down-regulation of tight junction protein expression in vascular endothelial cells promotes the extravasation of plasma components (such as coagulation factors and inflammatory mediators), activates microglia and triggers a neuroinflammatory cascade reaction. Based on the anatomical distance between WMH and the lateral ventricle, WMH can be classified into PVWMH and DWMH[28]. WMH 3-13mm away from the lateral ventricle was defined as PVWMH, while those larger than 13mm were defined as DWMH[29]. PVWMH is related to inflammation and chronic hemodynamic disorders, while DWMH is associated with demyelination, gliosis, etc. [25]. PVWMH is mainly supplied by the ventricular vessels originating from the subventricular artery or the terminal branch of the striatal artery, while DWMH is supplied by the medullary artery originating from the cortical branch of the middle cerebral artery. PVWMH and DWMH differ in pathogenesis and histopathology. Therefore, it is necessary for us to discuss the two separately.

## 5. OSAHS and WMH

The potential pathogenic mechanisms of WMH include factors such as ischemia-hypperfusion, inflammation, and subsequent demyelination. In patients with OSAHS, due to long-term apnea and IH, the cerebral blood flow velocity usually increases first. However, after resuming normal breathing, the cerebral blood flow velocity drops sharply. WMH is highly sensitive to changes in cerebral blood flow and pressure. Therefore, patients with OSAHS are more prone to WMH[30].

Studies have found that IH related to OSAHS can activate the sympathetic nerve, leading to cerebral vascular self-regulation disorders and promoting the occurrence and development of WMH [31]. Other studies have pointed out that IH can damage the integrity of white matter fibers in the brain. With the aggravation of the degree of OSAHS, the damage of white matter fibers intensifies [32]. Most current studies use the Fazekas scale to measure WMH. The Fazekas scale may have subjective errors in visual scoring, thereby causing result bias. Therefore, we used the UBO Detector white matter segmentation software to calculate the TWMH volume, PVWMH volume, and DWMH volume of patients with OSAHS, in order to quantify the WMH volume more accurately and explore the differences in WMH volume among patients with different degrees of OSAHS.

## 6. Hydrogen proton magnetic resonance spectroscopy (1H-MRS)

The research on neuroimaging methods has enabled humanity to take another important step forward in understanding the brain structure and function of patients with OSAHS. Neuroimaging further complicates more traditional sleep assessment techniques (such as polysomnography [15]) by providing unique information about brain structure, function and metabolite composition. Neuroimaging can help identify neural abnormalities related to vascular function in patients with OSAHS, and also assist researchers in identifying those OSAHS patients with a higher prognostic risk by examining the relationship between brain integrity and the functional response to treatment [33]. 1H-MRS is a non-invasive neuroimaging technique that can study the chemical activity of neuronal cells by detecting neurotransmitters and amino acids. The brain metabolites including NAA, Cho and Cr can be detected by 1H-MRS technology. 1H-MRS distinguishes different chemical shifts by using the slight differences in nuclear resonance frequencies under different chemical environments, thereby identifying different chemical substances and their contents. The Cr peak is at 3.05ppm. Due to its relative stability, Cr is often used as a control for metabolite ratios (such as NAA/Cr) [34]. The NAA peak is at 2.02ppm. It is generated in the mitochondria of neurons and transported to the cytoplasm of neurons. In clinical practice, NAA is often regarded as an indicator of neuronal density and viability. NAA also exists in immature oligodendrocytes and astrocyte progenitor cells. NAA is reduced in brain swelling, degenerative and destructive brain injury [35]. The Cho peak is at 3.20ppm, mainly derived from free choline, glycerol phosphocholine and phosphocholine. As part of the cell membrane, they are fixed. When they move, it indicates that the cell membrane is damaged. Therefore, Cho is a sign of membrane integrity [36]. A decrease in the ratio of NAA/Cr to NAA/Cho and an increase in the ratio of Cho/Cr often suggest the presence of varying degrees of brain neuron injury.

## 7. OSAHS and 1H-MRS

The research on neuroimaging methods has taken human understanding of the brain structure and function of patients with OSAHS to an important level again. 1H-MRS is a useful neuroimaging tool for studying OSAHS, which can provide unique information about brain structure, function and metabolite composition, including neuronal/axonal activity, cell metabolism and membrane state [37-38]. The study by Kamba et al. [35] showed that the NAA/Cr ratio in patients with severe OSAHS was significantly lower than that in patients with mild to moderate OSAHS, and the decrease in the NAA/Cr ratio might be caused by insufficient cerebral perfusion in patients with severe OSAHS. Furthermore, Algin et al.[38] found that there was a correlation between the severity of OSAHS and the NAA/Cho ratio, and the NAA/Cho ratio was significantly decreased in patients with severe OSAHS. Compared with patients with mild OSAHS, the Cho/Cr ratio of patients with severe OSAHS increased significantly. The increase in the Cho/Cr ratio may be related to insufficient cerebral perfusion [39]. MRS Provides a new direction for clarifying the pathogenesis of OSAHS-related cognitive impairment from the perspective of brain metabolism.

## 8. Conclusion

As mentioned earlier, OSAHS is a common but often overlooked disease with potential serious complications, mainly due to its significant cardiovascular and neurocognitive sequelae. Therefore, it is an important public health issue. Since the early symptoms of OSAHS patients are not obvious, thorough medical history inquiry and accurate use of diagnostic tests are particularly important. Finally, we should have a correct understanding of OSAHS and try to reduce the complications of OSAHS in patients to improve people's quality of life.

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