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Cognitive Impairment and Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) is a frequent sleep disorder characterized by repetitive interruption of ventilation caused by partial or complete collapse of the upper airway during sleep. OSA is highly prevalent in the world and it has been associated with cardiovascular disease and cognitive impairment in children and adults. The cognitive impairment in individuals with OSA includes deficiencies in attention and constructional abilities, delayed long-term visual and verbal memory, and executive functions. Although, the pathogenesis of cognitive impairment in patients with OSA is complex and remains incompletely understood, several mechanisms, such as hypoxia, inflammation and sleep fragmentation have been proposed. The aim of this chapter is to describe some findings reported in the literature to explain the association between OSA and cognitive impairment.

Keywords: obstructive sleep apnea, cognitive impairment, hypoxia, sleep fragmentation

1. Introduction

Obstructive sleep apnea (OSA) is a breathing disorder of sleep produced by partial or complete obstruction of the upper airways. This sleep disorder is characterized by breathing cessation and reduction of airflow resulting in temporary decrease, in cerebral oxygenation and sleep disruption [1]. The prevalence of OSA is approximately 10% in men and 3% in women between the ages of 30–49%, but rising to 17% in men older than 50 years and 9% in women post-menopause. It has been reported that prevalence of OSA has increased since 1990 in the United States and other countries. However, 80% of individuals with OSA remain undiagnosed and untreated [2].

The pathophysiology of OSA includes oxygen desaturation, alteration in sleep architecture and abnormal ventilation [3]. Hypoxemia and sleep fragmentation (arousals) cause excessive daytime sleepiness increasing the risk of road and work accidents [4] and reduced quality of life [5]. Additionally, OSA increase the risk of cardiovascular, cerebrovascular and metabolic diseases [6], neurocognitive impairment [7] and death [8]. One at time, cardiovascular diseases and metabolic consequences of OSA increase the risk of cognitive impairment. Cognitive deficits in individuals with OSA include attention and vigilance, episodic memory, delayed long-term visual and verbal memory, visuospatial/constructional abilities and executive functions [9–11]. Some studies reported that psychomotor function and

language do not seem compromised, [12] whereas others demonstrated to psychomotor function is affected by OSA and this domain does not improve with CPAP therapy [13]. Although the cognitive impairment in individuals with OSA is largely recognized as mild cognitive impairment, [14] OSA has also recognized as modifiable risk for dementia, neuropsychiatric disorders and stroke [15, 16]. However, the pathophysiology of cognitive impairment in adults with OSA is complex and the whole mechanisms involved in cognitive deficit have not been clarified yet.

2. Sleep's role in memory

Since, Hervey de Saint Denys published *Les Rêves et les Moyens de les Diriger* in 1867, was established that sleep benefits the retention of memory [17]. Rosa Heine was the first person, in 1914, who demonstrated that learning before a period of sleep results in a lower rate of forgetfulness in the following 24 hours than learning before a period of wakefulness. These results demonstrated the importance of sleep for memory. Likewise, Ellenbogen et al. showed that sleep after learning benefits the consolidation of memories and strengthens the traces of memory against future interference. Current research findings show an active sleep role in the consolidation of memory, learning and brain plasticity [18].

Sleep is defined as “a natural and reversible state of reduced response to external stimuli and relative inactivity, accompanied by decreased consciousness” [19]. Sleep has four basic states, rapid eye movement (REM), no REM sleep 1 (N1), NREM sleep 2 (N2) and NREM sleep 3 (N3). Slow wave sleep (SWS) is observed in N3. In humans, SWS predominates in the early stages of the sleep and REM in the final period, alternating in a cyclic manner. In terms of memory, forming and recovering memories is a fundamental ability to achieve adaptation. Memory functions involved different process such as encoding, consolidation and retrieval. During encoding, the stimulus results in the formation of a new memory fragment that is stabilized in consolidation process avoiding forgetting and incorporating the memory into preexisting knowledge complexes. Consolidation occurs during SWS and REM sleep stabilizes transformed memories [20, 21]. Also, it has been suggested the possibility that cholinergic tone during delayed REM sleep is necessary for the successful consolidation of memory [22, 23].

Theories that propose a differential role of the sleep stages in memory are based on the “dual process hypothesis.” In this dual hypothesis, SWS has a benefit in the declarative memories of events, such as learning word lists, word pairs or spatial locations, and processing dependent on the hippocampus [24], while REM sleep, benefits the consolidation of non-declarative memories (related to procedural memory, including mirror tracing, priming, implicit memory, and the emotional modulation of memories). A complex learning task can often involve both procedural and declarative learning components (complex motor movements, language learning). Emotive and sensitive events are better evoked than neutral ones, due to stimuli of the amygdala in the process of coding in the hippocampus. Changes registered in REM sleep for patients with mood disorders and lived dreams, clarify the link between REM sleep and the increase in amygdala activity. This activity has been related with the emotive and sensitive recycling during this stage of sleep. REM sleep seems also to be related with strength and weakened of emotional memory [25]. Findings from electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) show activity in brain regions (hippocampal) correlated with REM and SWS sleep, following both declarative and procedural learning. Although other theories hypothesized that memory consolidation occurs during different sleep states [26], neural processes of memory consolidation have been

observed during sleep and wakefulness [27]. Additional findings show that sleep enhances memory performance in brain-damaged individuals, except in patients with Parkinson [23].

The effect of sleep on memory is lasting and adaptive. Coding and initial recovery depends on the integrity of the hippocampus. The beneficial effect of sleep is linked to the interaction between slow oscillatory activity during SWS, thalamo-cortical sleep spindles and spontaneous reactivations of hippocampal memory [28]. In humans, slow wave sleep is correlated with hippocampus-dependent memory and REM sleep is associated with emotional memory. Currently, it is considered that an active consolidation of memory is established specifically during sleep and originates from the reactivation of newly coded memory representations that are integrated into the long-term knowledge networks. Findings from fMRI suggest that the process of consolidation in declarative memory is gradual. Then, the early activity after learning is observed in hippocampal locations, and after reinforced during sleep, long-lasting changes of memories are observed in medial prefrontal cortical activity. REM and NREM sleep are important for preservation, integration, and recollection of episodic memory [29]. In summary, sleep enhances learning of skills, semantic, episodic and emotional memories and stimulates creativity.

Some factors such as age, psychiatric and neurodegenerative conditions, sleep disruption and sleep apnea impair episodic memory [30, 31]. In patients with OSA cognitive processing, memory, vigilance, divided attention and executive functioning are affected. These deficits are observed identifying decreased ability to digest information, decreased ability to register, store, retain, and retrieve information, inability to maintain attention over the time, inability to respond to more than one task or stimuli, disorganization, emotional lability, impulsivity and difficulty maintaining motivation [32]. Beyond physiologic functions, the role of sleep in brain plasticity and memory consolidation processes is relevant, but the mechanisms involved in these processes remain to be fully understood. Therefore, it is necessary to perform future investigations to elucidate the pathophysiology of sleep disorders in neurocognitive impairment.

3. Physiopathology of cognitive impairment in obstructive sleep apnea

Neurocognitive impairment has over the years been associated with OSA but the prevalence of neurocognitive impairment in patients with OSA is not known [12]. One in four patients with OSA has neurophysiological impairment [33]. OSA patients are 7.5 to 20 times more likely to have difficulties with concentration, learning new tasks and execution monotonous tasks [34]. While current test for cognition not specifically assess impairments in OSA [35], some studies suggest that in the association between OSA and cognitive dysfunction, multitude of susceptibility and protective factors have been including, but others important factors should be considered. Susceptibility factors associated with neurocognitive impairment include: increased nocturnal awakenings, latency to REM sleep, [36, 37] changes in cerebral blood flow, neurovascular and neurotransmitter changes, intermittent hypoxemia, neuroinflammation, oxidative stress, ischemic precondition, hypercapnia [38, 39] and neural regulation in OSA [40]. Nevertheless, it is necessary to investigate the role of other factors such as genetic susceptibility, duration of OSA, hypertension, metabolic dysfunction, systemic inflammation, cerebral blood flow and blood-brain barrier [41].

Excessive daytime somnolence exhibit in patients with OSA increase the risk of cognitive decline and dementia. Sleep deprivation impair neuronal excitability, decrease myelination, produce cellular oxidative stress, misfolding of cellular

proteins, and alter molecular signaling pathways that regulate synaptic strength, plasticity-related gene expression and protein translation. These alterations create microinfarcts and brain atrophy that are associated with lower nocturnal oxygenation and reduction in NREM SWS sleep [42–44]. In OSA the proportion of stage N2 NREM sleep is increased and proportions of stages N1, N3 and REM sleep are decreased. During the NREM SWS abstraction of rules and integration of knowledge take place while in REM sleep creativity is benefited. In patients with OSA both sleep stages are reduced and fragmented, suggesting that some of the cognitive impairment is due to this dysregulation [45–47]. Frequently, obstructive events during NREM sleep have been associated with cognitive deficits and REM sleep events have been associated with greater sympathetic activity, hypertension and cardiovascular instability in patients with OSA. However, some studies reported that OSA reduction of REM sleep produce dissociation of REM traits to other sleep stages, affecting memory formation and consolidation [48, 49]. Gray matter atrophy in the prefrontal cortex observed in OSA and aging can mediate the degree of SWS disruption and consequent impaired overnight episodic hippocampal memory. Although several models have been proposed to explain the pathophysiology of cognitive impairment in OSA patients, the exact mechanisms of this association remain elusive [40, 50].

It has been suggested in meta-analysis and systematic review that cognitive deficit in patients with OSA is the result of poor night-time sleep and changes in the brain. Hypoxemia produces alteration of the prefrontal cortex and other CNS regions [51]. Then, global cognitive function is associated with hypoxemia and attention and vigilance dysfunction with sleep fragmentation. Sleep fragmentation is produced by the frequent sleep arousals that associated with apneic episodes contribute to abnormal sleep architecture, less restorative sleep and increased daytime sleepiness [14]. Therefore, treatment with continuous positive airway pressure (CPAP), should improve cognition and sleepiness. Evidence from clinical trials demonstrate that CPAP improves attention, vigilance memory executive functions and sleepiness, but deficits in learning memory and psychomotor function persist [52]. These findings suggest that improvements in sleepiness is not always associated with improvements in cognition, and it has been suggested that the improvement of cognition could be related with duration and severity of OSA [53].

Large-scale, multicenter, randomized, double-blind cohort study, the Apnea Positive Pressure Long-term Efficacy Study (APPLES), investigated the effects of CPAP on cognitive function in patients with OSA [53]. In this study, patients with severe OSA improved more than those with mild OSA. Although attention/psychomotor and learning/memory functions did not improve at either the 2-month or 6-month follow-up, improvement in the verbal delayed recall test was observed in patients on CPAP for 6 hours a day. Therefore, it was suggested that long-term memory deficits might be reversible with optimized CPAP treatment. Other studies following 3 and 12 months of treatment with CPAP show changes in gray frontal and hippocampal regions) and white matter correlated with improvements in memory, attention and executive functions [54, 55].

While several studies show that CPAP improves some cognitive domains, other studies reported less responsive for psychomotor activities. Additionally, the relationship between cognitive impairment and OSA severity is complex and the findings are inconsistent [9]. This complexity is represented by individual differences, genetic profiles and difficulties to measure OSA severity and cognitive impairment. Sleepiness questionnaire scores are not objectives and AHI (apnea/hypopnea index,

number of apnea and hypopnea events per hour of sleep) cannot measure the individual differences in the length of each event. Furthermore, oxygen desaturation index cannot identify the sleep cycle when hypoxia and arousal occur. Therefore, novel measures that separate sleep fragmentation and oxygen desaturation and measures to identify these events in each sleep cycle because cognitive functions are related with sleep cycles are needed [41].

Several factors contribute to individual differences in the relationship between OSA and cognition. Aging is associated with changes in morphology, size and reflex sensitivity of upper airway, resulting in a reduction in upper airway dilator muscle function at sleep in older people [56, 57]. Also, it has been suggested that co-morbidities such as hypertension, hyperlipidemia, diabetes, metabolic syndrome, and Alzheimer disease are the primary causes of the neurological damage. Other individual differences are related with genetic predisposition, mood, changes in macro and microcirculation in the brain, gender and experience of sleepiness [58].

4. Brain changes associated with OSA

There is evidence of structural and functional brain changes in critical areas for cognition in patients with OSA. Numerous investigations have reported changes in the electroencephalogram of OSA patients compared with healthy individuals. These changes show abnormal cortical excitability associated with neurocognitive deficits [59, 60]. In the prefrontal model sleep disruption, intermittent hypoxemia, and hypercapnia observed in OSA produce cellular and biochemical stresses that alter neuronal and glial viability within prefrontal regions of the brain cortex, affecting the efficacy of restorative process occurring during sleep. This model explains the relationship between sleep fragmentation and nocturnal hypoxemia with predominantly frontal deficits. However, the neuroanatomic regions that have most commonly been reported in OSA are thalamus and frontoparietal cortex [61]. Degenerative areas in brain include: hippocampus (memory and new learning), the thalamus (sensory and motor signaling and in regulating sleep and alertness) and the amygdala (regulation of emotion) [16]. The findings in fMRI suggested a dysfunctional connectivity of the posterior default mode neuronal network and changes in network in the anterior insula, posterior-medial frontal cortex and thalamus (right amygdala-hippocampus complex and the insular cortex) [62, 63].

Several studies reported that OSA is a risk factor for cerebral small vessel disease (C-SVD). C-SVD is a group of pathologic processes that affect small arteries and veins, arterioles, and capillaries. Restricted blood flow in diseased small vessels, produce low perfusion pressure and hypoperfusion of the affected brain areas. Subsequently, chronic hypoperfusion develop ischemic C-SVD [64, 65]. Changes in white matter associated with OSA has also been reported. Degradation of multiple areas of subcortical tracts of the superior and inferior parietal lobe, deep frontal white matter and arcuate fasciculus. The white matter fiber integrity was recuperated after 12 months of CPAP treatment and this recuperation was associated with improvement in memory, attention, and executive functions [55]. The gray matter is also affected in patients with OSA. Some studies report that extent of gray matter volume loss increases correlated positively with OSA severity. Decreased gray matter has been observed in the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum [66, 67] (**Figure 1**).

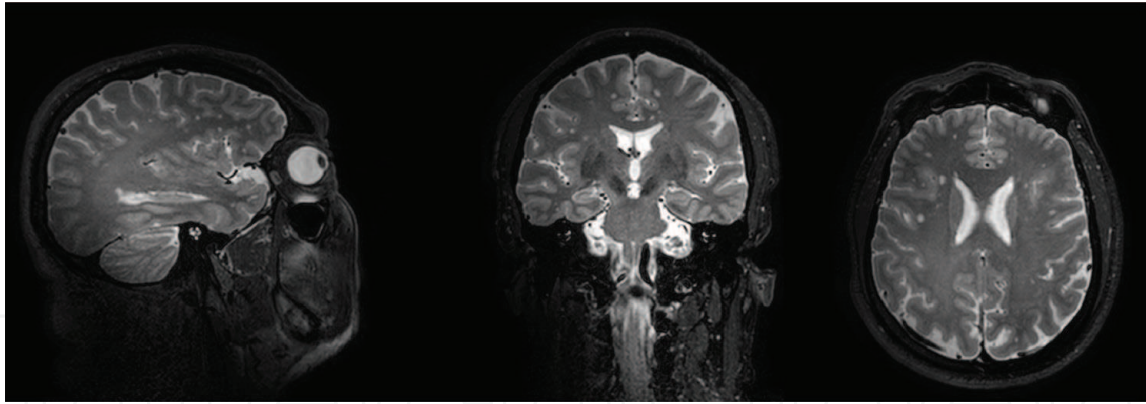


Figure 1.
Magnetic resonance imaging in patient with cognitive impairment and OSA and in healthy individual.

5. Mechanisms associated to cognitive impairment in OSA

OSA causes oxygen desaturation producing arousals and nocturnal intermittent hypoxemia. The intermittent hypoxia is linked to cerebral microvascular and neurovascular changes. Several models have been proposed to explain the pathophysiology of neurocognitive impairment in patients with OSA. Some of these models include: prefrontal model sleep disruption, neuroinflammatory process, hypoperfusion and endothelial dysfunction. Neuroinflammatory process is one of the mechanisms proposed to explain the association between OSA and cognitive impairment. Healthy microglia of central nervous system (CNS) show a surveillance phenotype that synthesizes neuroprotective growth factors. In OSA ischemic condition activates several genes including vascular endothelial growth factor (VEGF), erythropoietin, atrial natriuretic peptide (ANP), hypoxia inducible factor-1 (HIF-1), and brain-derived neurotrophic factor (BDNF) [68]. Altered resting cerebral blood flow pattern and hypoperfusion in several CNS regions have been demonstrated in patients with OSA during sleep and awake states [69]. Repetitive hypoxia and reoxygenation promote oxidative stress producing blood-brain barrier hyperpermeability and neuroinflammation. These alterations result in plasma proteins leaking into the arteriolar walls and perivascular spaces (Virchow-Robin spaces) and subsequent accumulation of macrophages and fibrosis in the arteriolar walls leading to the development or progression of C-SVD. Severe and prolonged hypoxia can activate microglia toward a toxic, pro-inflammatory phenotype causing white matter damage and lacunar infarction and accumulation of plasma proteins in the small arterial walls. Additionally, inflammation at the blood-brain barrier alters the transport of molecules across the barrier, resulting in progressive synaptic plasticity and neuronal dysfunction. This maladaptive neuroinflammatory process, observed in patients with OSA, increases hippocampal apoptosis, impaired synaptic plasticity, and cognitive impairment [70–74].

In hypoperfusion model, the cognitive impairment is explained in this way: in normal conditions the cerebral autoregulation mechanism protects the brain through maintaining cerebral perfusion during blood pressure changes. In OSA this system is impaired because of changes in nocturnal intracranial hemodynamics and oxygen saturation, resulting in cerebral hypoperfusion in the regions with poor collateral circulation. Chronic hypoperfusion in small arteries and arterioles leads to ischemic changes in white and gray matter. Although cerebral blood flow is increased to compensate for oxygen desaturation in patients with OSA, this mechanism is not enough and the chronic hypoxemia promotes the progression of C-SVD resulting in lacunar infarcts, white matter abnormalities and gray matter

loss. Damage to prefrontal and frontal lobes, basal ganglia and hippocampus are associated with abnormal myelin and axonal integrity. Prolonged hypoxic–ischemic damage to the frontal and prefrontal cortex is associated with executive dysfunction in patients with moderate to severe OSA, but this damage could improve with CPAP treatment [75–79].

In endothelial dysfunction model, neurocognitive impairment is produced for several mechanisms. The apneic episodes cause repetitive intracranial blood flow impairing the endothelial cells of small arteries and arterioles and decreasing endothelial vasodilator production. Nitric oxide regulates cerebral blood flow in response to hypercapnia, but in OSA nitric oxide is decreased, and the vasodilatory capacity of cerebral vasomotor reactivity in response to hypercapnia is compromised. Altered cerebral vasomotor reactivity associated with poor microvascular blood flow produce white matter lesions. Additionally, disruption of nitric oxide pathways causes a cascade of neuronal metabolic deficiencies, resulting in destabilizing neurons, synapses, and neurotransmission, and generating synaptic loss and neuronal damage [80–83].

Investigations about the impact of patients with OSA treated with CPAP in the cognitive function have showed that daytime sleepiness decrease and cognitive function improves. The amount of improvement depends of biologic variability present in each patient [55, 84, 85]. Previous studies had been demonstrated that sleep disruption impaired cognitive function and the mechanisms of cognitive harm in OSA and chronic obstructive pulmonary disease (COPD) are similar. However, the pathophysiology of neurocognitive impairment in OSA and insomnia seems to be different, and the cognitive deficit in individuals with OSA is greater [46, 85, 86]. Therefore, other mechanisms such as changes in the brain could explain the cognitive impairment associated with OSA. Additionally, in some patients with OSA cognitive deficit persist, even after prolonged treatment with CPAP. For this reason, it is necessary to design future studies to identify appropriate treatment that can be administered before irreversible atrophic and metabolic changes occur [41, 87, 88]. Further studies should be performed to elucidate mechanisms of neurocognitive impairment and to identify genetics profiles for prediction of neurocognitive effects of CPAP in patients with OSA and other comorbidities.

6. Conclusions

- Obstructive sleep apnea is associated with cognitive impairment and is a modifiable risk factor for dementia.
- Sleep fragmentation, hypoxia, maladaptive pathways, neuroinflammation, hypoperfusion and endothelial dysfunction contribute with neurocognitive impairment in patients with OSA.
- Future studies should be conducted to identify novel diagnosis and therapeutic tools for OSA and cognitive impairment.
- The exact pathophysiology of cognitive impairment in OSA patients remain elusive as the role of therapy for OSA on cognitive impairment.

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