

# Neurocognitive Decline in Obstructive Sleep Apnea: An Ignored Entity

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## ABSTRACT

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder causing cognitive dysfunction. Unfortunately, both the disease itself and this disastrous complication go unnoticed due to poor perception for the same. This review attempts to explain the pathophysiology, consequences, and treatment options for the same. The keypoint is early diagnosis and treatment of OSA so as to prevent the cognitive decline.

**Keywords:** Continuous positive airway pressure, Neurocognitive, Obstructive sleep apnea.

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## INTRODUCTION

Obstructive sleep apnea (OSA) is a common, yet underdiagnosed sleep-related breathing disorder with significant adverse health consequences. OSA is characterized by a recurrent, functional collapse of the velopharyngeal, and/or, oropharyngeal airway, causing reduced or complete cessation of airflow despite ongoing breathing efforts. This leads to intermittent disturbances in gas exchange (e.g., hypercapnia and hypoxemia) and arousal from sleep, usually at the termination of the apneic episode, resulting in sleep fragmentation and changes in neural activity: all of which are potential mechanisms for the cognitive difficulties that occur in OSA.<sup>1</sup>

Prevalence estimates vary according to the way in which OSA is defined and the distribution of risk factors in the population being studied. The prevalence of sleep disordered breathing (SDB) was 19.5% and that of obstructive sleep apnoea hypopnoea syndrome (OSAHS) was 7.5% in healthy urban Indian males between 35 and 65 years of age.<sup>2</sup> In adults, OSA prevalence rises markedly with age. Between the ages of 30 and 49 years, 10% of men and 3% of women are diagnosed, rising to 17% and 9%, respectively, for 50–70-year-old.<sup>3,4</sup> This is critical because the longer OSA goes untreated, the greater the risk of hypertension,<sup>5</sup> heart disease,<sup>6</sup> stroke,<sup>7</sup> kidney disease,<sup>8</sup> type 2 diabetes mellitus,<sup>9</sup> and motor vehicle accidents.<sup>10</sup> The metabolic and vascular consequences, in turn, increase the severity of OSA and the risk of both cognitive impairment and dementia, and potentially bring forward the age of onset of mild cognitive impairment and Alzheimer's disease (AD).<sup>11</sup>

OSA is associated with excessive daytime sleepiness, inattention, and fatigue, which may impair daily function, induce, or exacerbate cognitive deficits, and increase the likelihood of errors and accidents. Systematic and meta-analytic reviews provide robust evidence that OSA impacts neurocognitive functions. Sleep fragmentation or the subsequent daytime sleepiness is among the most important etiologies related to the decline of neurocognitive function in OSA patients.<sup>12</sup>

Continuous positive airway pressure (CPAP) is the most efficacious and widely used medical treatment of OSA, since it improves daytime sleepiness and neurocognitive dysfunction.<sup>13</sup>

To date, the literature on the effect of CPAP on the extent of reversing cognitive deficits, duration of use required for it, and domains of cognition it impacts the most in OSA remains contradictory and sparse

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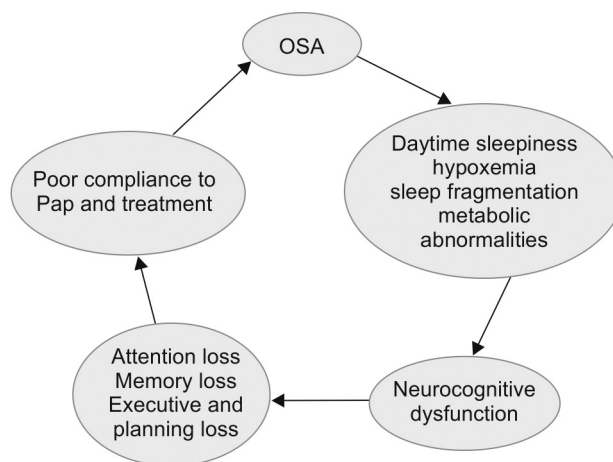
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## IMPACT OF OSA ON COGNITION

OSA leads to neurocognitive dysfunction which begets OSA like a vicious and never-ending cycle (Fig. 1). Cognitive functions include memory, attention, language, executive function, besides, and visuospatial/constructional abilities.<sup>14</sup> A meta-analysis concluded that all these functions are impacted by OSA.<sup>15</sup>



**Fig. 1:** Vicious cycle of neurocognitive dysfunction in obstructive sleep apnea which can be broken by early diagnosis and appropriate positive airway pressure therapy

Neurocognitive impairment, ultimately, has an unfavorable effect on patients' productivity at work and social safety and quality of life.<sup>16</sup>

### Attention

It is the most common impaired cognition in OSA. It has been categorized as divided, selective, and sustained attention.<sup>17</sup> Several studies have demonstrated that drivers with OSA have decreased visual vigilance/sustained attention, which is closely associated with sleep fragmentation/disorder-related daytime sleepiness and tiredness, and they have an increased risk of road traffic accidents.<sup>18</sup> Studies have also shown that OSA patients have difficulty in involuntary attention switching.<sup>19</sup> Damage due to loss of attention has a positive association with the OSA severity.<sup>20</sup>

### Memory

OSA is associated with both short-term and working memory deficits, which has been pathophysiologically linked to the hypoxic changes in the hippocampus.<sup>21</sup> One study suggests that only verbal memory was impaired in OSA patients.<sup>22</sup> However, there is evidence of visual memory loss also.<sup>23</sup> A meta-analysis concluded that immediate and delayed recalls, both, were affected in terms of visuospatial and verbal episodic memory.<sup>24</sup>

### Executive Functions

Executive function is as vulnerable to damage as other cognitive functions. This includes loss of fluid reasoning, shifting, and inhibition. A meta-analysis demonstrated that the entire function of planning, working memory, phonological fluency, and cognitive flexibility have been impaired in OSA patients.<sup>25</sup>

## PATHOPHYSIOLOGY BEHIND COGNITIVE DYSFUNCTION

### Excessive Sleepiness

Excessive sleepiness can account for a majority of the neurocognitive deficits in OSA, and its role may even be more than that of hypoxias.<sup>26,27</sup> Attention deficits may be a result of sleep fragmentation, again, leading to excessive daytime sleepiness.<sup>28,29</sup>

### Desaturation

The old literature documents hypoxia as the principal underlying pathophysiology of cognitive dysfunction.<sup>30</sup> Hypoxemia may be the trigger for neuronal injury in OSA patients.<sup>31</sup> In fact, studies have shown that neurocognitive performance correlates with the severity of hypoxemia.<sup>32,33</sup> Dysfunction of the prefrontal cortex can adversely affect executive functioning.<sup>34</sup>

### Sleep Fragmentation

Sleep fragmentation and daytime sleepiness in OSA influence all the aspects: attention and memory and executive dysfunction.<sup>27,34,35</sup> An international epidemiological survey of over 10,000 patients also concluded the same.<sup>36</sup>

### Metabolic Factors

Metabolic disturbance of lipid and protein can contribute to cognitive impairment.<sup>16</sup> Pediatric OSA with cognitive dysfunction have been found to have a lower concentration of serum insulin-like growth factor (IGF).<sup>37</sup> Besides, the increased rate of APOE ε4 allele indicates a hereditary link for neurocognitive impairment in OSA.<sup>38</sup>

## EVIDENCE FROM IMAGING

Advancements in neuroimaging have helped to understand the structural changes in brain structure in cognitive dysfunction. This has recently been also evaluated for OSA patients.

### Magnetic Resonance Imaging (MRI)

Inverse correlation between the ratio of gray matter volume to total brain volume and the visual-fine motor coordination score has been demonstrated using 3D-MRI images of the brain in children.<sup>32</sup>

### Functional MRI (fMRI)

Reduction in brain activation in cingulate, frontal, and parietal regions was found in OSA patients.<sup>38</sup> Similarly, decreased activation in the prefrontal cortex was found to be associated with impaired executive function.<sup>39</sup>

### Magnetic Resonance Spectroscopy (MRS)

An old study found frontal white matter metabolic abnormalities in OSA patients.<sup>40</sup> However, lately, focal reductions in frontal gyrus, hippocampus, and parietal cortex have shown correlation with cognitive impairments.<sup>41</sup>

The emerging evidence that gray matter density changes may precede an objective neurocognitive decline in OSA that has triggered a search for markers which can be used in future for screening.<sup>42</sup> In addition, the response of these changes after CPAP therapy gives rise to the concept of neuroplasticity and the partially reversible features of this neurocognitive dysfunction.<sup>41</sup>

## TREATMENT

CPAP prevents airway collapse, improves respiratory pattern, prevents hypoxia, and corrects sleep fragmentation in OSA. This, in turn, improves daytime sleepiness and neurocognitive dysfunction. The literature supports the response of CPAP for all severities of OSA across all time periods of use in improving excessive daytime sleepiness.<sup>43</sup>

A meta-analysis reported improvement in objective daytime wakefulness [maintenance of wakefulness test (MWT)] with CPAP but no change in objective daytime sleepiness [multiple sleep latency test (MSLT)] in mild OSA.<sup>43</sup> Several studies have shown that CPAP corrects nocturnal hypoxemia, sleep quality, sleepiness and cognition; the effects being more subjective and higher in severe OSA.<sup>44-47</sup>

CPAP has shown to partly reversed neurocognitive deficits after 3–6 months of use in OSA with excessive daytime sleepiness. The improvement was in attention, vigilance, verbal and visual memory, delayed long-term executive dysfunction, and global cognitive function, but, these were small sample size studies.<sup>48-50</sup> A recent large multicenter trial also reported a transient improvement in frontal-lobe and executive function in severe OSA patients after CPAP.<sup>51</sup>

However, not all the cognitive functions improve with CPAP. A study concluded that while most executive functions improve, short-term memory impairment persists.<sup>52</sup> Another study demonstrated no dose–response effect of CPAP in the improvement of verbal memory loss.<sup>53</sup> It has been suggested that this may be due to irreversible chronic hypoxic cerebral damage, particularly in frontal lobes. Besides, the cognitive decline may also be multifactorial and, hence, not reversible.<sup>53</sup>

There are very few studies to study the role of CPAP in OSA without daytime sleepiness evaluating the effect of CPAP on OSA patients without EDS. A randomized controlled trial reported

no benefit in cognitive function (vigilance, memory, attention, information processing) in OSA with the use of CPAP.<sup>54</sup>

## CONCLUSION

OSA is a common cause of neurocognitive dysfunction which can be best prevented by early diagnosis and institution of therapy in the form of PAP devices. CPAP has even shown to be partly reverse this neurocognitive decline. Hence, a high index of suspicion should be kept for diagnosing neurocognitive dysfunction in all patients of OSA.

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