The impact of sleep and hypoxia on the brain: potential mechanisms for the effects of obstructive sleep apnea

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INTRODUCTION
Obstructive sleep apnea (OSA) is a prevalent, chronic and multisystem disease, which can concomitantly lead to acute clinical issues. These can include systemic or pulmonary hypertension, cardiovascular disease, glucose intolerance, impotence, gastroesophageal reflux and a variety of neuropsychiatric and cerebrovascular deficits [1–5]. Population-based studies suggest that up to 19% of middle-aged men and 15% of women may suffer with hypopnoea and apneas above the normative index, the majority of which are undiagnosed [6,7].

OSA is characterized by the narrowing or occlusion of the pharyngeal airway, which can be caused by a myriad of risk factors, for example, macroglossia, hypertrophy of tonsils, long uvula, increased neck circumference, postmenopausal status, Down’s syndrome, Pierre–Robin syndrome, alcohol consumption before bedtime, tobacco and hypnotic use, supine position, etc. The nocturnal episodes of complete or partial pharyngeal obstruction result in intermittent hypoxia, reoxygenation, hypercapnia...
KEY POINTS

- OSA is a highly prevalent multisystem disease that can lead to distinct CNS injury and associated functional deficits in some patients.
- The two major culprits of OSA-induced brain injury are thought to be intermittent hypoxia and sleep fragmentation.
- During nocturnal apnoeic and hypopneic episodes, pathways are initiated in the CNS that may result in enhanced brain plasticity and cerebrovascular responses, as well as adaptive mechanisms such as ischemic preconditioning.

The effects of CPAP use can be extended to minimally (MOSAIC and PREDICT) suggest that the beneficial (CNS) manifestation [6,13,14]. Two recent studies appear as the leading central nervous system somnolence, and in some, neurological deficits. However, not all patients with OSA report daytime OSA and symptoms of excessive sleepiness [12,13]. One of the most effective treatments of OSA is the continuous positive airway pressure therapy (CPAP). It consists of an air pressure generating device and a close fitting mask that maintains upper airway patency and prevents airway obstruction with associated sleep fragmentation [6]. Currently, the National Institute of Clinical Excellence guidelines recommend CPAP as the cost-effective treatment of choice for patients with moderate-to-severe OSA and symptoms of excessive sleepiness [12,13]. However, not all patients with OSA report daytime somnolence, and in some, neurological deficits appear as the leading central nervous system (CNS) manifestation [6,13,14]. Two recent studies (MOSAIC and PREDICT) suggest that the beneficial effects of CPAP use can be extended to minimally symptomatic, and older OSA patients, respectively [14,15**]. Understanding the efficacy and cost-effectiveness of OSA treatment is increasingly important, as OSA is predicted to become a highly prevalent health problem in the future, because of the rise of its two most prominent risk factors, obesity and older age [3,5].

The Neuropathology of Obstructive Sleep Apnea

During obstructive apneas, changes in cerebral blood flow occur [16] and apnea-induced hypoxemia combined with reduced cerebral perfusion likely predisposes patients to nocturnal cerebral ischemia [17,18]. In addition, hypoperfusion during the awake states [19] with altered resting cerebral blood flow pattern in several regions has been shown in OSA [19]. Numerous clinical studies demonstrate changes in the electroencephalogram of OSA patients, including aberrant cortical excitability [20–23] and an associated array of neurocognitive deficits. Taken collectively they also delineate a putative neurocircuitry fingerprint of OSA-induced brain injury and suggest the disruption of the (cerebello)-thalamocortical oscillator with involvement of the hippocampal formation [9,21–23]. It has been previously suggested that a constellation of symptoms frequently encountered in OSA patients, such as depression, disturbances in attention, dysmetria of thought and affect, executive and verbal memory deficits [24–26], point to similarities with the spectra of two other well recognized neurological clinical syndromes, thalamocortical dysrhythmia and cerebellar cognitive affective syndrome [9,27,28]. Correspondingly, the neuroanatomical regions most commonly reported in clinical and animal studies as affected in OSA suggest that both the cerebellar modulation of neural circuits and the normal state-dependent flow of information between thalamus (and basal ganglia) and frontoparietal cortex are likely to be affected in susceptible patients [10,29–35] (Fig. 1).

Additionally, several other neuropsychiatric disorders are frequently reported comorbid or closely associated with OSA [26]. For example, adults with epilepsy appear at increased risk of OSA [36]. Similarly, OSA is associated with seizure exacerbation in older adults with epilepsy, and treatment with CPAP may represent an important avenue for improving seizure control in this population [37,38]. Sleep apnea is also a recognized independent risk factor for stroke [39–41]. It is believed to exacerbate neural damage during the stroke, as well as to increase the risk of a subsequent stroke [5,42]. Moreover, an increasing body of evidence from animal studies suggests that cerebral amyloidogenesis and tau phosphorylation, two cardinal features of Alzheimer’s disease, can be triggered by intermittent hypoxia [1]. Intermittent hypoxia and reactive oxygen species, known to occur during nocturnal apnoeic episodes, were shown to initiate neuronal degeneration and axonal dysfunction in cortex and brainstems of animals [1]. Also, the oligodendrocytes, myelin-producing cells of the CNS, were shown as selectively sensitive to hypoxia and sleep fragmentation [43]. However, it is not clear to what extent this particular vulnerability contributes to the widely reported hypotrophic white matter.
changes (e.g., fornices and corpus callosum) in the brains of some OSA patients [35,44,45]. However, and in line with preclinical findings, several clinical studies also suggested that older patients with OSA suffer accelerated brain atrophy, cognitive decline and the onset and severity of dementia [2,5,8,46]. Conversely, in children with OSA, diminished learning capabilities, increased hyperactivity and incidence of attention-deficit disorders have all been documented [8]. Unique periods of susceptibility during the life-span, along with genetic, environmental and lifestyle conditions, appear to determine the severity of the intermittent hypoxia effects on the CNS [15**,26,47]. Some of these effects at both ends of the age spectrum may also reflect the direct and epigenetic impact of intermittent hypoxia during the heterochronus neurodevelopmental myelination process. This process in humans, unlike that in other primates, spans several decades and likely contributes to later-life cognitive gains [48,49].

Notwithstanding the above-mentioned changes, OSA-associated brain injury is commonly reported as subtle [50], its associated neurocognitive deficits as mild and diffuse, and their full or partial reversibility by the CPAP is debatable [8*,9,24,26,30,50–53]. The root of this discrepancy is attributed to the use of different image analysis methods in various studies over the years, varied statistical thresholds and lack of an OSA-specific battery of sensitive neurocognitive tests [50]. Additionally, the interindividual heterogeneity to a given hypoxic stimulus during OSA [54] and the effects of sleep on regional neuronal vulnerability are thought to contribute to this variability [8*,9,35]. Similarly, the cardiovascular and cerebrovascular protection conferred by ischemic preconditioning resulting from the nocturnal cycles of hypoxia-reoxygenation is thought to play an important role [35,54,55].

**OBSTRUCTIVE SLEEP APNEA AND THE ISCHAEMIC PRECONDITIONING**

Ischemic preconditioning represents a generalized adaptation to ischemia by a variety of cells [54,56]. It has been proposed that OSA represents a clinical example of preconditioning and the development

![Image](image_url)

**FIGURE 1.** Neuroanatomical changes in obstructive sleep apnea. Localized grey matter loss is shown in the right temporal lobe and cerebellum of OSA patients compared with healthy controls (a). Reproduced with permission from [30]. An aberrant, likely compensatory, interregional connectivity between hippocampus and cerebellum was demonstrated in OSA patients (b). CC, cerebellar cortex; H, hippocampus; L, left; OSA, obstructive sleep apnea; R, right; r, Pearson correlation coefficient. Reproduced with permission from [35].
of adaptive responses to intermittent hypoxia [55]. In OSA, induction of ischemic preconditioning is thought to be due to the activation of several gene programs, including the hypoxia inducible factor-1, vascular endothelial growth factor, erythropoietin, atrial natriuretic peptide and brain-derived neurotrophic factor [55,57]. Over the years, various endomerenchiasms and pathways have been suggested and/or shown to play a role, including that of long-term facilitation of phrenic motor output, chemoreflex activation, vascular remodelling, neoangiogenesis, productive autophagy, reactive gliosis, various synaptic alterations, and more recently modulation of neurogenesis has also been suggested [4,58–61]. Chronic intermittent hypoxia and sleep fragmentation, the two major architects of OSA-induced injury in the CNS, can both decrease hippocampal neurogenesis in rodents [62,63]. However, hypoxic and ischaemic insults are also recognized stimulators of adult neurogenesis [64].

Gozal et al. [62] demonstrated increased proliferation in the dentate gyrus of the hippocampus at a later stage of exposure to intermittent hypoxia, which was present despite the ongoing noxa. They subsequently suggested that biphasic, temporal change in dentate gyrus proliferation accounted for the partial recovery of clinical function in the later stages of this process. Accordingly, other preclinical studies have demonstrated the protective nature of moderate intermittent hypoxia, supporting the notion that ischemic preconditioning-like processes occur [4,65]. For example, in a rodent model, the intermittent hypoxia intervention before the ischemic event leads to increased expression of brain-derived neurotrophic factor, increased neurogenesis and functional synaptogenesis, as well as to improvement in spatial learning and long-term memory impairment [59,60]. In another study, intermittent hypoxia in adult rats was shown to promote hippocampal neurogenesis and mimic antidepressant-like effects [66]. However, it is of note that these studies also suggested that the duration of the exposure to intermittent hypoxia and the intensity of the hypoxia and associated oxidative stress were important determinants of whether intermittent hypoxia was protective or harmful [4,61,67].

Hippocampal formation is known as the ‘limbic’ core of the affected neurocircuitry loop in OSA [10,31,51,68–70]. The hippocampus interacts with other regions of brain, inclusive of thalamus [71] and cerebellum [72], via two major gateway systems: the entorhinal cortex and the fimbria fornix pathway [73,74]. Hippocampal function varies in a subregion-specific fashion: spatial processing likely occurs in the dorsal hippocampus, whereas anxiety-related behaviour relies on the ventral region [75–78] (Fig. 2).

It is critically involved in learning and memory and its connectivity with prefrontal and parietal regions regulates a variety of attentional, memory and emotional processes [75,79]. CPAP treatment of OSA has been shown to partially reverse the damage in this region and to ameliorate some of the associated functional deficits, possibly also by modulating the hippocampal neurogenesis [51]. However, the results of this study are yet to be repeated and further research is required.

Conditioned central neurogenic neuroprotection has been shown following the activation of the intrinsic neurons of the cerebellar fastigial nucleus [80]. Neurostimulation of these nuclei appears to provide ‘protective’ reduced excitability of cortical neurons during the subsequent ischemic episodes and to lead to reduced immunoreactivity of cerebral microvessels. The ‘compensatory’ entraining of cerebellum by hypertrophic hippocampi was proposed to occur in some younger patients with mild OSA [35]. Although there are no direct monosynaptic anatomical connections between hippocampi and cerebellum, their connectivity is thought to be important for the control of movement under states of heightened emotion, novel conditions and for the associative learning. Hippocampus is connected to cerebellum via the pontine, reticular and olivary nuclei, whereas the return loop is via the fastigial nucleus and thalamus [72]. Recently, a role for hippocampal theta oscillations has been proposed in coordination of a widely distributed memory system for associative learning, of which cerebellum is a part [81] (Fig. 2). Moreover, some studies suggest that hippocampal theta oscillations, also thought to play the role in hippocampal neurogenesis [74], can modulate the functional properties of the cerebellum [81] (Fig. 2).

In a recent neuroimaging study, coexistence of hypotrophic (e.g., corpus callosum) and hypertrophic (e.g., hippocampi volumes and cerebellar functional connectivity) changes in OSA patients was also demonstrated [35]. It was argued that these changes may reflect the evolving nature of the OSA-associated brain injury and an intricate and dynamic interaction of various noxious events and neuroinflammation alongside workings of the endogenous repair systems in the brain, such as ischemic preconditioning and enhanced brain plasticity [35,56,74,82,83].

**OBSTRUCTIVE SLEEP APNEA AND THE DISTURBANCE OF SLEEP STRUCTURE**

Frequent partial sleep arousals are, along with intermittent hypoxia and hypercapnia, the core features
of OSA [8,9]. They contribute to abnormal sleep architecture, lighter, less restorative sleep and symptoms of excessive daytime somnolence. The experts in the field are divided as to the true consequences of disturbed sleep.

The new, and somewhat controversial, synaptic homeostasis hypothesis (SHY) proposes that sleep is the price that the brain pays for plasticity [84]. The role of sleep, its slow wave components, REM activation and sleep spindles, in preserving the brain plasticity by renormalizing net synaptic strength and restoring cellular homeostasis, is one of the least well understood terra incognita’s of today’s translational neuroscience. Correspondingly, comparatively little is known about the neuromechanisms of OSA-induced brain injury, likely exerted via repeated arousals disturbing different stages of sleep [9]. It has been found that stage N2 of non-rapid-eye movement (nREM) sleep increases in OSA patients, whereas stages N1, N3 and REM sleep decrease [6]. Furthermore, several recent clinical studies suggest disturbed spatiotemporal evolution of sleep spindles in patients with OSA during the night [23,85].

Pleomorphic animal studies suggest that sleep fragmentation independently affects similar CNS regions to those affected by the intermittent hypoxia [8*]. In a similar manner, clinical studies of the effects of sleep deprivation on cognition in the general population suggest comparable impairments to those seen in OSA [86]. Traditionally, the highest impact has been reported on cognitive systems that rely on emotional data [86]. In patients with OSA, the notion is that modulation of various

FIGURE 2. Schematic presentation of putative theoretical neuromechanisms of some of the plastic changes noted in clinical studies of obstructive sleep apnea patients. Theta (θ) is the archetypical rhythmic activity in hippocampus that runs from the dentate gyrus-to CA3/CA1-to entorhinal cortex [74]. Hippocampal θ is thought to modulate the functional properties of the cerebellum and to govern hippocampal neurogenesis [74]. A decrease in θ band occurs post apnea and hypopnoea events in some OSA patients [22]. CPAP normalizes these electroencephalogram changes [20]. ‘Hypofunctioning’ fornix likely alters dentate gyrus neurogenesis and possibly also contributes to mild cognitive decline in OSA [73,77]. CPAP, continuous positive airway pressure; DG, dentate gyrus; OSA, obstructive sleep apnea. Adapted with permission from [78].
neurotransmitters (e.g., noradrenaline) occurs during sleep, and this might also alter hippocampal-amygdalar-based learning [8,97]. In addition, and perhaps in wider agreement with SHY and other theories of memory and sleep, a number of clinical and community-based studies suggest that obstructive events during rREM sleep are associated with greater cognitive deficits or impaired quality of life [88]. On the other hand, REM sleep events appear to be associated with greater sympathetic activity and cardiovascular instability in patients with OSA [88].

CONCLUSION

The preceding paragraphs briefly summarize our current understanding of the putative relationships between the distinctive type and distribution of neuropathology in OSA and associated functional changes. It is clear that OSA-induced brain injury depends on the specific individual clinical parameters and the stage of pathological process [89,90]. Thus far, distinct aspects of the OSA functional ‘neuroconnectivity fingerprint’ are yet to be fully understood [89]. Further clinical studies should utilize multimodal approach to enable more reliable referencing for the acuity of the pathological process, as well as its reversibility following the treatment.

Clearly, early detection of the CNS sequelae in OSA is vital in order that prompt treatment can be administered before the full syndromic constellation of symptoms manifest. On a mechanistic level, further investigations of the interplay between various sleep stages and severity of OSA could further inform our understanding of accelerated cognitive decline in older OSA patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


A comprehensive review of the current knowledge of effects on the brain.


A recent multicentre randomised trial which suggests the beneficial effects of CPAP in elderly OSA patients.


68. Kilgore WD. Effects of sleep deprivation on cognition. Prog Brain Res 2010; 185:105–129.

69. Frank MG. Erasing synapses in sleep: is it time to be SHY? Neural Plast 2012; 2012:64378.


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