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

Ivana Rosenzweig[a,b], *Steve C.R. Williams*[a], *and Mary J. Morrell*[a,c,d]

Purpose of review
Obstructive sleep apnea (OSA) is a chronic, highly prevalent, multisystem disease, which is still largely underdiagnosed. Its most prominent risk factors, obesity and older age, are on the rise, and its prevalence is expected to grow further. The last few years have seen an exponential increase in studies to determine the impact of OSA on the central nervous system. OSA-induced brain injury is now a recognized clinical entity, although its possible dual relationship with several other neuropsychiatric and neurodegenerative disorders is debated. The putative neuromechanisms behind some of the effects of OSA on the central nervous system are discussed in this review, focusing on the nocturnal intermittent hypoxia and sleep fragmentation.

Recent findings
Recent preclinical and clinical findings suggest that neurogenic ischemic preconditioning occurs in some OSA patients, and that it may partly explain variability in clinical findings to date. However, the distinct parameters of the interplay between ischemic preconditioning, neuroinflammation, sleep fragmentation and cerebrovascular changes in OSA-induced brain injury are still largely unclear, and more research is required.

Summary
Early diagnosis and intervention in patients with OSA is of paramount importance. Future clinical studies should utilize multimodal investigative approaches to enable more reliable referencing for the acuity of the pathological process, as well as its reversibility following the treatment.

Keywords
central nervous system, intermittent hypoxia, ischaemic preconditioning, obstructive sleep apnea, sleep fragmentation

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

[a]Sleep and Brain Plasticity Centre, Department of Neuroimaging, Institute of Psychiatry, King's College and Imperial College London, UK, [b]Danish Epilepsy Centre, Dianalund, Denmark, [c]Academic Unit of Sleep and Breathing, National Heart and Lung Institute, Imperial College London and [d]NIHR Respiratory Disease Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, London, UK

Correspondence to Dr Ivana Rosenzweig, Department of Neuroimaging, Box 089, Institute of Psychiatry, De Crespigny Park, King's College London, London, SE5 8AF, UK. Tel: +44 203 228 3084; e-mail: ivana1.rosenzweig@kcl.ac.uk

Curr Opin Pulm Med 2014, 20:565–571
DOI:10.1097/MCP.0000000000000099

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.

and sleep fragmentation [8▪,9]. An increase in respiratory effort, in association with hypoxia or hypercapnia, triggers the frequent sleep arousals, which usually terminate the apnoeic episodes, but also contribute to abnormal sleep architecture and lighter and less restorative sleep [10]. Reduced quality of life, labile interpersonal relationships, increased road traffic accidents, and decreased work and school efficiency have all been reported in OSA patients [11]. However, the most widely recognized symptom of OSA is excessive daytime sleepiness [6].

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

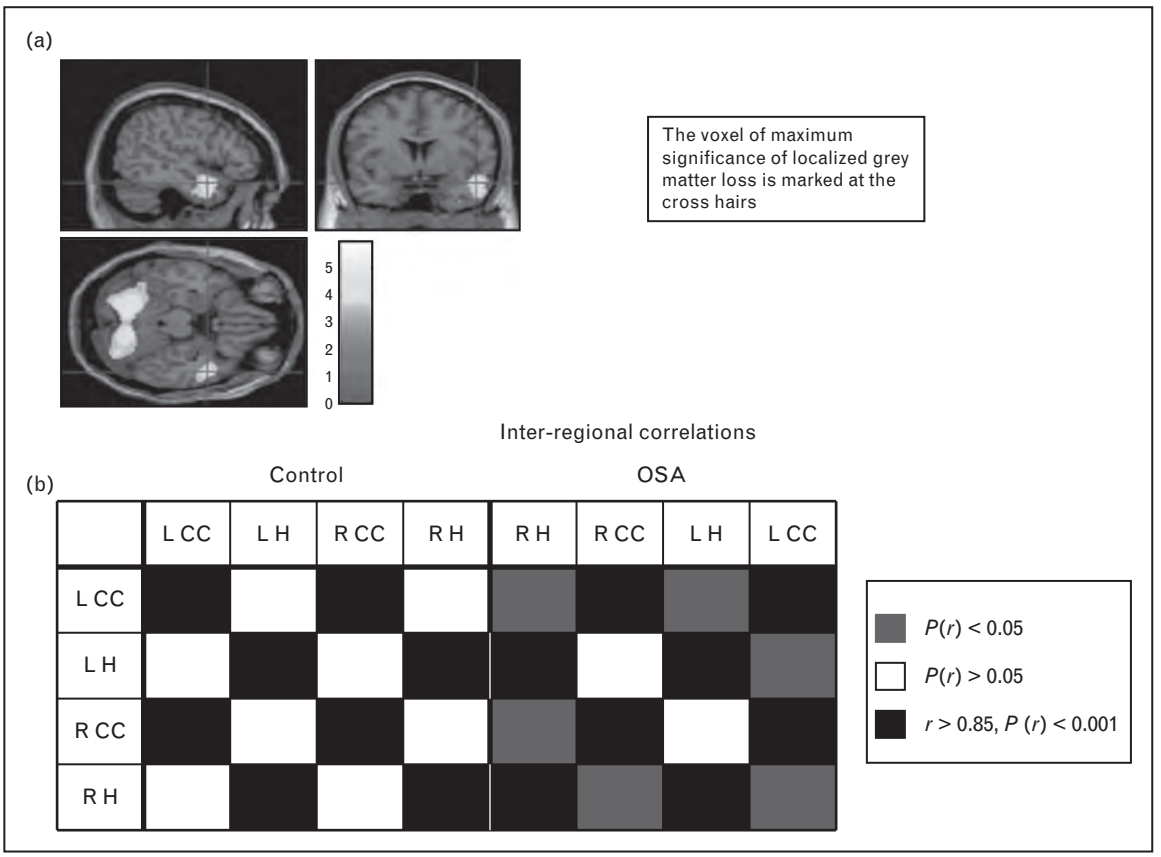

FIGURE 1. Neuroanatomical changes in obstructive sleep apnea. Localized grey matter loss is shown in the right temporal lobe and cerebellum of OSA patients compared with healthy controls (a). Reproduced with permission from [30]. An aberrant, likely compensatory, interregional connectivity between hippocampus 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].

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 lifespan, 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

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 end-mechanisms 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 noxius 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

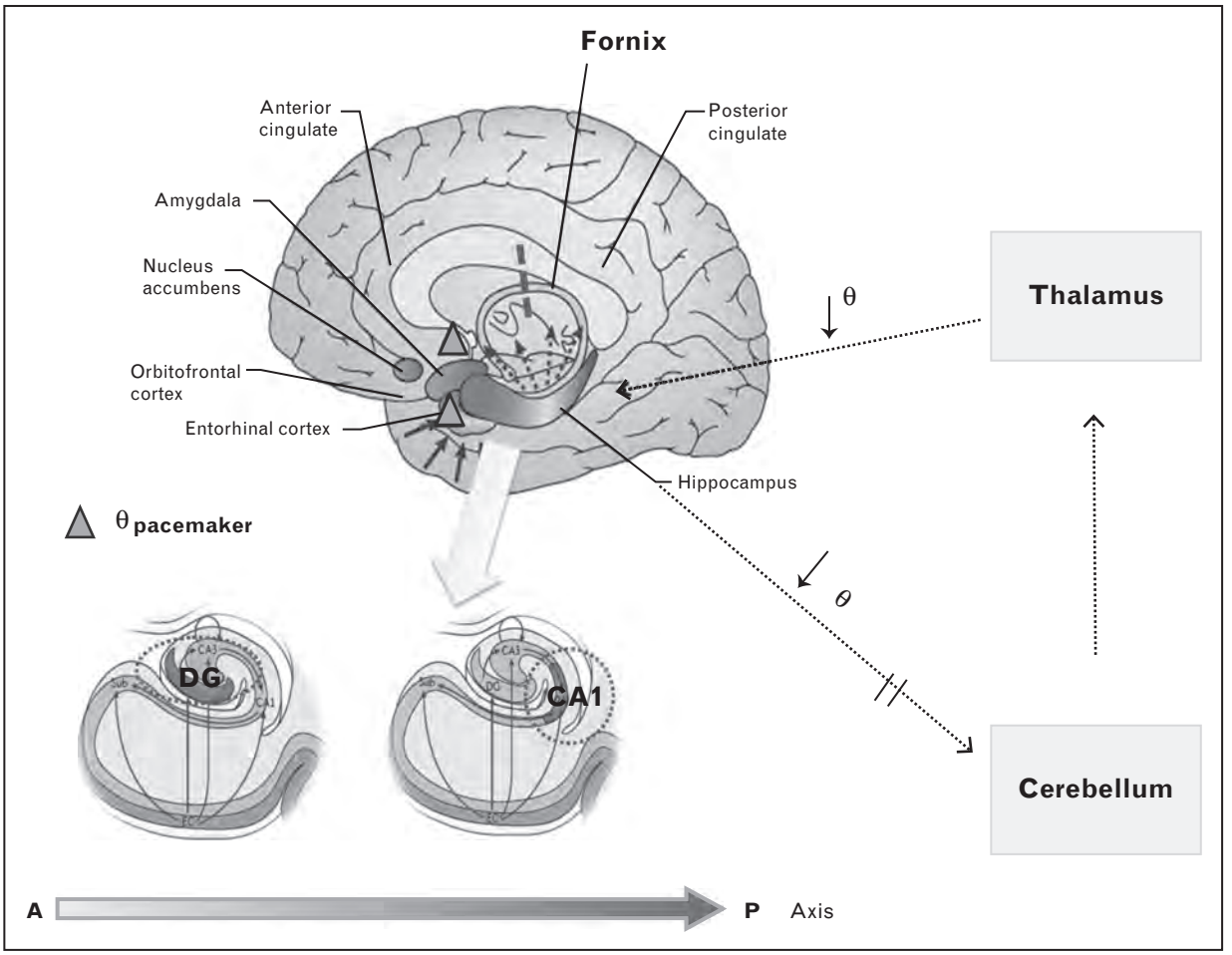

FIGURE 2. Schematic presentation of putative theoretical neuromechanisms of some of the plastic changes noted in clinical studies of obstructive sleep apnea patients. Theta (θ) is the archetypical rhythmic activity in hippocampus that runs from the dentate gyrus-to CA3/CA1-to entorhinal cortex [74]. 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].

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].

Pleiomorphic 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

neurotransmitters (e.g., noradrenaline) occurs during sleep, and this might also alter hippocampal-amygdalar-based learning [9,87]. 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 nREM 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]. Future 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.

Acknowledgements

This work was supported by the Wellcome Trust [103952/Z/14/Z] and the NIHR Respiratory Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust, Imperial College London. The authors apologize to all the colleagues whose outstanding work could not be cited due to space limitations.

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

1. Daulatzai MA. Death by a thousand cuts in Alzheimer's disease: hypoxia: the prodrome. Neurotox Res 2013; 24:216–243.
2. Ayalon L, Ancoli-Israel S, Drummond SP. Obstructive sleep apnea and age: a double insult to brain function? Am J Respir Crit Care Med 2010; 182:413–419.
3. Li Y, Veasey SC. Neurobiology and neuropathophysiology of obstructive sleep apnea. Neuromolecular Med 2012; 14:168–179.
4. Haddad GG, Yu SP. Brain hypoxia and ischemia: with special emphasis on development. New York: Humana Press; 2009; xi, pp. 343.
5. Durgan DJ, Bryan RM Jr. Cerebrovascular consequences of obstructive sleep apnea. J Am Heart Assoc 2012; 1:e000091.
6. Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. Sleep Disord 2014; 2014:768210.
7. Young T, Palta M, Dempsey J, *et al.* The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–1235.
8. ■ Gozal D. CrossTalk proposal: the intermittent hypoxia attending severe obstructive sleep apnoea does lead to alterations in brain structure and function. J Physiol 2013; 591 (Pt 2):379–381.

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

9. Rosenzweig I, Williams SC, Morrell MJ. CrossTalk opposing view: the intermittent hypoxia attending severe obstructive sleep apnoea does not lead to alterations in brain structure and function. J Physiol 2013; 591 (Pt 2):383–385.
10. Joo EY, Tae WS, Lee MJ, *et al.* Reduced brain gray matter concentration in patients with obstructive sleep apnea syndrome. Sleep 2010; 33:235–241.
11. Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnoea. Sleep Med Rev 1999; 3:59–78.
12. McDaid C, Griffin S, Weatherly H, *et al.* Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. Health Technol Assess 2009; 13:iii–iv.
13. McDaid C, Duree KH, Griffin SC, *et al.* A systematic review of continuous positive airway pressure for obstructive sleep apnoea-hypopnoea syndrome. Sleep Med Rev 2009; 13:427–436.
14. Craig SE, Kohler M, Nicoll D, *et al.* Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax 2012; 67:1090–1096.
15. ■■ McMillan A, Bratton DJ, Faria R, *et al.* A 12 month multicentre, randomised trial of continuous positive airway pressure in older people with obstructive sleep apnea syndrome. Lancet Resp Med 2014. [Epub ahead of print]. doi: 10.1016/S2213-2600(14)70172-9.

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

16. Hajak G, Klingelhofer J, Schulz-Varszegi M, *et al.* Sleep apnea syndrome and cerebral hemodynamics. Chest 1996; 110:670–679.
17. Meadows GE, Kotajima F, Vazir A, *et al.* Overnight changes in the cerebral vascular response to isocapnic hypoxia and hypercapnia in healthy humans: protection against stroke. Stroke 2005; 36:2367–2372.
18. Balfors EM, Franklin KA. Impairment of cerebral perfusion during obstructive sleep apneas. Am J Respir Crit Care Med 1994; 150 (6 Pt 1):1587–1591.
19. Joo EY, Tae WS, Han SJ, *et al.* Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. Sleep 2007; 30:1515–1520.
20. Morisson F, Decary A, Petit D, *et al.* Daytime sleepiness and EEG spectral analysis in apneic patients before and after treatment with continuous positive airway pressure. Chest 2001; 119:45–52.
21. Morisson F, Lavigne G, Petit D, *et al.* Spectral analysis of wakefulness and REM sleep EEG in patients with sleep apnoea syndrome. Eur Respir J 1998; 11:1135–1140.
22. Dingli K, Assimakopoulos T, Fietze I, *et al.* Electroencephalographic spectral analysis: detection of cortical activity changes in sleep apnoea patients. Eur Respir J 2002; 20:1246–1253.
23. Schonwald SV, Carvalho DZ, de Santa-Helena EL, *et al.* Topography-specific spindle frequency changes in obstructive sleep apnea. BMC Neurosci 2012; 13:89.
24. Twigg GL, Papaioannou I, Jackson M, *et al.* Obstructive sleep apnea syndrome is associated with deficits in verbal but not visual memory. Am J Respir Crit Care Med 2010; 182:98–103.
25. Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. Prog Brain Res 2011; 190:53–68.
26. Sforza E, Roche F. Sleep apnea syndrome and cognition. Front Neurol 2012; 3:87.
27. Llinas RR, Ribary U, Jeanmonod D, *et al.* Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 1999; 96:15222–15227.
28. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121 (Pt 4):561–579.
29. Macey PM, Henderson LA, Macey KE, *et al.* Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002; 166:1382–1387.
30. Morrell MJ, Jackson ML, Twigg GL, *et al.* Changes in brain morphology in patients with obstructive sleep apnoea. Thorax 2010; 65:908–914.
31. Morrell MJ, McRobbie DW, Quest RA, *et al.* Changes in brain morphology associated with obstructive sleep apnea. Sleep Med 2003; 4:451–454.
32. Yaouhi K, Bertran F, Clochon P, *et al.* A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 2009; 18:36–48.

33. O'Donoghue FJ, Briellmann RS, Rochford PD, *et al.* Cerebral structural changes in severe obstructive sleep apnea. Am J Respir Crit Care Med 2005; 171:1185–1190.
34. Kumar R, Farahvar S, Ogren JA, *et al.* Brain putamen volume changes in newly-diagnosed patients with obstructive sleep apnea. Neuroimage Clin 2014; 4:383–391.
35. Rosenzweig I, Kempton MJ, Crum WR, *et al.* Hippocampal hypertrophy and sleep apnea: a role for the ischemic preconditioning? PLoS One 2013; 8:e83173.
36. Foldvary-Schaefer N, Andrews ND, Pornsriniyom D, *et al.* Sleep apnea and epilepsy: who's at risk? Epilepsy Behav 2012; 25:363–367.
37. Pornsriniyom D, Shinlapawittayatorn K, Fong J, *et al.* Continuous positive airway pressure therapy for obstructive sleep apnea reduces interictal epileptiform discharges in adults with epilepsy. Epilepsy Behav 2014; 37C:171–174.
38. Chihorek AM, Abou-Khalil B, Malow BA. Obstructive sleep apnea is associated with seizure occurrence in older adults with epilepsy. Neurology 2007; 69:1823–1827.
39. Redline S, Yenokyan G, Gottlieb DJ, *et al.* Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010; 182:269–277.
40. Yaggi HK, Concato J, Kernan WN, *et al.* Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005; 353:2034–2041.
41. Munoz R, Duran-Cantolla J, Martinez-Vila E, *et al.* Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006; 37:2317–2321.
42. Somers VK, White DP, Amin R, *et al.* Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008; 118:1080–1111.
43. Bellesi M, Pfister-Genskow M, Maret S, *et al.* Effects of sleep and wake on oligodendrocytes and their precursors. J Neurosci 2013; 33:14288–14300.
44. Macey PM, Kumar R, Yan-Go FL, *et al.* Sex differences in white matter alterations accompanying obstructive sleep apnea. Sleep 2012; 35:1603–1613.
45. Kumar R, Pham TT, Macey PM, *et al.* Abnormal myelin and axonal integrity in recently diagnosed patients with obstructive sleep apnea. Sleep 2014; 37:723–732.
46. Fotuhi M, Hachinski V, Whitehouse PJ. Changing perspectives regarding late-life dementia. Nat Rev Neurol 2009; 5:649–658.
47. Kim J, Bhattacharjee R, Khalyfa A, *et al.* DNA methylation in inflammatory genes among children with obstructive sleep apnea. Am J Respir Crit Care Med 2012; 185:330–338.
48. Bartzokis G. Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments. Front Biosci (Landmark Ed) 2011; 16:2695–2733.
49. Rosenzweig I, Vukadinovic Z, Turner AJ, Catani M. Neuroconnectivity and valproic acid: the myelin hypothesis. Neurosci Biobehav Rev 2012; 36:1848–1856.
50. Morrell MJ, Glasser M. The brain in sleep-disordered breathing: a vote for the chicken? Am J Respir Crit Care Med 2011; 183:1292–1294.
51. Canessa N, Castronovo V, Cappa SF, *et al.* Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med 2011; 183:1419–1426.
52. Canessa N, Ferini-Strambi L. Sleep-disordered breathing and cognitive decline in older adults. JAMA 2011; 306:654–655.
53. Kushida CA, Nichols DA, Holmes TH, *et al.* Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep 2012; 35:1593–1602.
54. Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. Med Hypotheses 2006; 66:1069–1073.
55. Brzecka A. Brain preconditioning and obstructive sleep apnea syndrome. Acta Neurobiol Exp (Wars) 2005; 65:213–220.
56. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol 2009; 8:398–412.
57. Nanduri J, Yuan G, Kumar GK, *et al.* Transcriptional responses to intermittent hypoxia. Respir Physiol Neurobiol 2008; 164 (1–2):277–281.
58. Papadakis M, Hadley G, Xilouri M, *et al.* Tsc1 (hamartin) confers neuroprotection against ischemia by inducing autophagy. Nat Med 2013; 19:351–357.
59. Tsai YW, Yang YR, Sun SH, *et al.* Post ischemia intermittent hypoxia induces hippocampal neurogenesis and synaptic alterations and alleviates long-term memory impairment. J Cereb Blood Flow Metab 2013; 33:764–783.
60. Tsai YW, Yang YR, Wang PS, Wang RY. Intermittent hypoxia after transient focal ischemia induces hippocampal neurogenesis and c-Fos expression and reverses spatial memory deficits in rats. PLoS One 2011; 6:e24001.
61. Aviles-Reyes RX, Angelo MF, Villarreal A, *et al.* Intermittent hypoxia during sleep induces reactive gliosis and limited neuronal death in rats: implications for sleep apnea. J Neurochem 2010; 112:854–869.
62. Gozal D, Row BW, Gozal E, *et al.* Temporal aspects of spatial task performance during intermittent hypoxia in the rat: evidence for neurogenesis. Eur J Neurosci 2003; 18:2335–2342.
63. Sportiche N, Suntsova N, Methippara M, *et al.* Sustained sleep fragmentation results in delayed changes in hippocampal-dependent cognitive function associated with reduced dentate gyrus neurogenesis. Neuroscience 2010; 170:247–258.
64. Lichtenwalner RJ, Parent JM. Adult neurogenesis and the ischemic forebrain. J Cereb Blood Flow Metab 2006; 26:1–20.
65. Jung ME, Simpkins JW, Wilson AM, *et al.* Intermittent hypoxia conditioning prevents behavioral deficit and brain oxidative stress in ethanol-withdrawn rats. J Appl Physiol (1985) 2008; 105:510–517.
66. Zhu XH, Yan HC, Zhang J, *et al.* Intermittent hypoxia promotes hippocampal neurogenesis and produces antidepressant-like effects in adult rats. J Neurosci 2010; 30:12653–12663.
67. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia - ■ Revisited - The bad ugly and good: implications to the heart and brain. Sleep medicine reviews 2014. [Epub ahead of print]. doi: 10.1016/j.smrv.2014.07.003.
A comprehensive review of the current knowledge of effects of intermittent hypoxia, oxidative stress and the radical oxygen species on the brain and heart.
68. O'Donoghue FJ, Wellard RM, Rochford PD, *et al.* Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. Sleep 2012; 35:41–48.
69. Torelli F, Moscufo N, Garreffa G, *et al.* Cognitive profile and brain morphological changes in obstructive sleep apnea. Neuroimage 2011; 54:787–793.
70. Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the hippocampus with ageing. Nat Rev Neurol 2012; 8:189–202.
71. Zhang Y, Yoshida T, Katz DB, Lisman JE. NMDAR antagonist action in thalamus imposes delta oscillations on the hippocampus. J Neurophysiol 2012; 107:3181–3189.
72. Newman PP, Reza H. Functional relationships between the hippocampus and the cerebellum: an electrophysiological study of the cat. J Physiol 1979; 287:405–426.
73. Metzler-Baddeley C, Hunt S, Jones DK, *et al.* Temporal association tracts and the breakdown of episodic memory in mild cognitive impairment. Neurology 2012; 79:2233–2240.
74. Seki T. Neurogenesis in the adult brain. Tokyo; New York: Springer; 2011.
75. Bannerman DM, Rawlins JN, McHugh SB, *et al.* Regional dissociations within the hippocampus: memory and anxiety. Neurosci Biobehav Rev 2004; 28:273–283.
76. Bonnici HM, Chadwick MJ, Kumaran D, *et al.* Multivoxel pattern analysis in human hippocampal subfields. Front Hum Neurosci 2012; 6:290.
77. Macey PM, Kumar R, Woo MA, *et al.* Brain structural changes in obstructive sleep apnea. Sleep 2008; 31:967–977.
78. Small SA, Schobel SA, Buxton RB, *et al.* A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nature Rev Neurosci 2011; 12:585–601.
79. Plessen KJ, Bansal R, Zhu H, *et al.* Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2006; 63:795–807.
80. Reis DJ, Golanov EV, Galea E, Feinstein DL. Central neurogenic neuroprotection: central neural systems that protect the brain from hypoxia and ischemia. Ann N Y Acad Sci 1997; 835:168–186.
81. Hoffmann LC, Berry SD. Cerebellar theta oscillations are synchronized during hippocampal theta-contingent trace conditioning. Proc Natl Acad Sci U S A 2009; 106:21371–21376.
82. Lledo PM, Alonso M, Grubb MS. Adult neurogenesis and functional plasticity in neuronal circuits. Nat Rev Neurosci 2006; 7:179–193.
83. Ferriero DM. Protecting neurons. Epilepsia 2005; 46 (Suppl 7):45–51.
84. Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 2014; 81:12–34.
85. Carvalho DZ, Gerhardt GJ, Dellagustin G, *et al.* Loss of sleep spindle frequency deceleration in obstructive sleep apnea. Clin Neurophysiol 2014; 125:306–312.
86. Killgore WD. Effects of sleep deprivation on cognition. Prog Brain Res 2010; 185:105–129.
87. Frank MG. Erasing synapses in sleep: is it time to be SHY? Neural Plast 2012; 2012:264378.
88. Mokhlesi B, Punjabi NM. ''REM-related'' obstructive sleep apnea: an epiphenomenon or a clinically important entity? Sleep 2012; 35:5–7.
89. Gozal D. Rebuttal from david gozal. J Physiol 2013; 591 (Pt 2):387.
90. Macey PM. Is brain injury in obstructive sleep apnea reversible? Sleep 2012; 35:9–10.