Sleep apnoea and the brain: a complex relationship

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Intermittent hypoxia, reoxygenation, and hypercapnia or hypocapnia occur in both adults and children during untreated apnoea and hypopnoea, along with changes in cerebral blood flow and sleep fragmentation. These effects can result in cognitive deficits with functional effects on work and school efficiency. The assessment of how obstructive sleep apnoea affects cognition depends on the specificity and sensitivity of the tests, which are rarely developed specifically for obstructive sleep apnoea. In this Review, we discuss both the neural adaptive and maladaptive processes in response to hypoxaemia. The net result on cognitive and emotional performance depends on the stage of this dynamic process, effects on other body systems, cognitive reserve, and idiosyncratic susceptibility. We also explore the contribution of fragmented sleep, and the disruption of sleep structure, with focus on the effect at different times in the development of disease. This Review will address the gap in the underlying pathophysiology of new clinical and translational findings, and argue their contribution to the inherent complexity of the association between obstructive sleep apnoea and the brain.

Introduction
Obstructive sleep apnoea is a highly prevalent, chronic, multisystem disease that remains under recognised in the general population, despite the 20 years that have elapsed since the seminal prevalence report in 1993, and more than 30 years since the acclaimed account of the prevalence of obstructive sleep apnoea in the USA has more than 30 years since the acclaimed account of the prevalence of obstructive sleep apnoea.1–4 Epidemiological data suggest the prevalence of obstructive sleep apnoea in the USA has increased by 14–55% since the early 1990s.5 Similar prevalence has been noted in other countries and specific ethnic groups around the world, with clear overall male preponderance until menopause age in women.6–10 Obstructive sleep apnoea is usually associated with serious cardiovascular and metabolic comorbidities, with systemic hypertension occurring in up to 50% of patients with obstructive sleep apnoea.11,12 Strong associations of obstructive sleep apnoea with old age (used in this Review to refer to patients aged 65 years or over) and obesity, both of which are on the rise, underscore its important public health implications.11,13

The syndromic constellation of effects of obstructive sleep apnoea on the brain merit particular attention and are the focus of this Review. This disorder is increasingly recognised as a potentially modifiable risk factor for dementia, especially in older adults.14–16 A role of obstructive sleep apnoea in seizure aggravation in epilepsy, several neuropsychiatric disorders, and stroke has also been proposed.7 The progressive changes in sleep quality and structure, along with changes in cerebral blood flow, neurovascular and neurotransmitter changes, cellular redox status, and neural regulation in patients with obstructive sleep apnoea could constitute a contributing factor to cognitive decline, which is also seen with healthy ageing but is present to a much greater extent in neurodegenerative diseases.17–19

Reduced quality of life, excessive daytime sleepiness, labile interpersonal relationships, increased road traffic accidents, and decreased work and school efficiency have all been reported in patients with obstructive sleep apnoea, and these effects are not always reversed with treatment.20 Beneficial effects of treatment on cognitive performance (including vigilance and sleepiness) and neural injury in this disorder (figure 1) have been documented in meta-analyses21,22 and a meta review.23 Findings from two studies21,23 likewise suggest beneficial effects of CPAP therapy in older people with obstructive sleep apnoea24 and in those with negligible symptoms.25 The dearth of fully effective treatments for the CNS sequelae of obstructive sleep apnoea is probably a reflection of poorly understood yet intricate interplay of intermittent hypoxia, reoxygenation, hypercapnia, changes in cerebral blood flow,26 and sleep fragmentation that result from nocturnal episodes of complete or partial pharyngeal obstruction in the disease.27

We and others have argued that both adaptive and maladaptive processes in response to hypoxaemia occur in the brains of patients with obstructive sleep apnoea. The overall result depends on the stage of this dynamic process, effects on other body systems, cognitive reserve, and the idiosyncratic susceptibility of each particular individual.

Key messages
• Obstructive sleep apnoea is a prevalent, chronic multisystem disease with a high socio-economic burden, which remains under diagnosed in the general population.
• Obstructive sleep apnoea is increasingly recognised as one of the potentially modifiable risk factors for dementia; its multiple effects on the central nervous system are acknowledged, although their nature and prognosis are yet to be fully understood.
• Both maladaptive and adaptive pathways are likely initiated in the central nervous system during nocturnal apnoeic and hypopnoeic episodes and ensuing sleep fragmentation, the net result of which will depend on the chronicity of process and idiosyncratic characteristics of each patient.
• In future, multimodal investigative approaches should help elucidate more reliable referencing for the acuity of the pathological process, as well as its reversibility following the treatment.
Impaired cognition in patients with sleep apnoea

Over the years, a broad range of psychological problems and neurocognitive impairments have been associated with obstructive sleep apnoea. However, some have argued that detailed analysis of important studies in the speciality supports only a weak association between subjective cognitive complaints in patients with obstructive sleep apnoea and their objective cognitive functioning. This argument has already been used to highlight different results of subjective versus objective complaints in other medical populations such as patients with cancer, and several possible explanations in patients with obstructive sleep apnoea have been suggested. For example, specificity of tests for cognitive deficits documented in obstructive sleep apnoea is largely acknowledged as variable. Objective tests for cognition are frequently designed to assess cognitive deficits in patients with brain injury and as such do not specifically assess impairments in obstructive sleep apnoea. Testing provides a snapshot of someone’s ability, and it is unlikely that it accurately assesses aspects of cognition in patients with obstructive sleep apnoea that are task dependent or time dependent. In view of the complex neuropathology of obstructive sleep apnoea, a snapshot value of a particular function or ability, as assessed by cognitive tests, might not fully account for its fluctuation over time and various daytime requirements. Cognitive domains are not unitary constructs, and only the carefully deconstructed analysis of their different subcapacities and their susceptibilities to a range of risks and protective factors specific to obstructive sleep apnoea can provide a more realistic assessment of cognitive deficits. Similarly, several impairments might be secondary to other symptoms of obstructive sleep apnoea, such as sleepiness, or might be a sign of psychological distress.

Non-pharmacological and some pharmacological treatments for obstructive sleep apnoea have been shown to improve cognitive outcomes in subpopulations of patients with the disorder. Several meta-analyses suggest that CPAP treatment reduces daytime sleepiness and mood problems, and improves objective cognitive function in patients with obstructive sleep apnoea. Many questions remain unanswered regarding treatment with CPAP, the most pivotal of which are who should receive this treatment, when, and for how long. The full prescriptive protocols, probably in combination with other lifestyle and pharmacological approaches, might only be achieved once the full range of neuropathological changes of obstructive sleep apnoea and its dynamic fingerprint (ie, characteristic dynamic changes in multimodal biomarkers) are understood. For example, the beneficial effect of CPAP on symptoms of sleepiness and quality of life in some patients seems to be obtained after only few days of treatment with good adherence, whereas the effects of CPAP on other subjective and objective cognitive symptoms are less well defined. Two studies report that prolonged treatment might be needed in some patients with severe symptoms. Findings from a study assessing compliance in patients with severe obstructive sleep apnoea showed almost complete recovery of white matter tract integrity with associated substantial improvement in memory, attention, and executive functioning at 2 years of follow-up. Findings of another small pilot study suggested the need for longer treatment with CPAP in elderly patients, and showed that treatment of severe obstructive sleep apnoea in patients with Alzheimer’s disease of mild to moderate severity is associated with much slower cognitive decline over 3 years compared with decline in patients not treated with CPAP. Although less striking, evidence from studies of donepezil, physostigmine, and fluticasone suggests better cognitive
outcomes in patients with obstructive sleep apnoea treated with these drugs.\textsuperscript{42} So far, subjective cognitive complaints have been largely ignored in randomised trials of treatments for obstructive sleep apnoea. In line with the findings discussed in this Review, and because subjective cognitive complaints are known to be linked to quality of life, work productivity, and health-care use in the general population, future studies should take these complaints into account.\textsuperscript{11}

Some investigators have argued against a reductionist approach to obstructive sleep apnoea-induced brain injury, and point out that emerging research suggests that the association between disease severity and cognitive dysfunction is the product of many susceptibility and protective factors, of which sleep fragmentation, hypoxia, and cognitive reserve are just three aspects.\textsuperscript{23,25,31} Some other important factors are duration of disease, the role of the blood–brain barrier, hypertension, metabolic dysfunction, systemic inflammation, cerebral blood flow, and genetic susceptibility (eg, apolipoprotein e4 genotype).\textsuperscript{12}

Most studies in the specialty so far point to substantial deficits in attention and vigilance, visuospatial and constructual abilities, executive dysfunction, and delayed long-term visual and verbal memory in patients with obstructive sleep apnoea.\textsuperscript{24,24} Several associations have been recognised: the association between worsening general cognitive functioning and severity of hypoaxemia; and the association between dysfunction of attention and vigilance and degree of sleep fragmentation.\textsuperscript{24} Consensus is less strong on the effects of obstructive sleep apnoea on working memory and short-term memory.\textsuperscript{24} Language ability and psychomotor functioning have been largely unaffected by obstructive sleep apnoea in some studies,\textsuperscript{24} whereas others\textsuperscript{45} have pointed to psychomotor slowing as the most susceptible cognitive domains, and least responsive to treatment with CPAP. Similar results from several studies\textsuperscript{24,45} have shown impairments in language abilities in patients with severe obstructive sleep apnoea, but have not agreed on whether phonemic or semantic domains are those most affected.\textsuperscript{31} Neurodevelopmental stages of adolescents and children with obstructive sleep apnoea seem to dictate higher risk for language deficit.\textsuperscript{45}

The functional neuroanatomy of obstructive sleep apnoea has been further highlighted in a 3 month study of CPAP treatment, which showed improved cognitive function in several domains that corresponded to an increase in grey matter volume in frontal and hippocampal regions.\textsuperscript{7} Similarly, findings from another study showed great improvements in memory, attention, and executive functioning that were associated with the white matter changes after 12 months of treatment with CPAP.\textsuperscript{50} Most studies investigating treatments for obstructive sleep apnoea have not accounted for incomplete reversal of tissue damage or deficits in cognition, suggesting that initiation of prolonged treatment might be needed as early as possible in the disease process.\textsuperscript{46,50}

Results of studies investigating the cognitive performance and effects of treatment in children with obstructive sleep apnoea are similar.\textsuperscript{41,42} In a study of children with sleep disordered breathing, followed up for 4 years, treatment led to improvements in several aspects of neurocognition, collectively classified as performance IQ.\textsuperscript{51} Performance IQ represents fluid intelligence that is indicative of incidental learning and describes one’s ability to adapt to new situations.\textsuperscript{52} In this study, improvements were recorded in tasks associated with spatial visualisation, visuo-motor coordination, abstract thought, and non-verbal fluid reasoning.\textsuperscript{51} However, overall improvements in academic ability or behaviour were less clearcut. Worsening of verbal IQ, which, unlike performance IQ, is more likely to be affected by formal education and learning experiences, was noted in a treated group.\textsuperscript{51} However, a definitive explanation for this finding was not provided, and no significant association between the reduction in verbal IQ performance and treatment was seen.\textsuperscript{51} Conversely, a study in which younger children with sleep disordered breathing were followed up for 12 months of CPAP treatment showed substantial improvement in academic performance.\textsuperscript{51} The different neuro-developmental ages of children, and different test variables used, provided a complex clinical dataset from which no definite conclusions can be drawn. Nevertheless, particular patterns and associations seem to be emerging from this and earlier studies,\textsuperscript{23,54} among which the association between performance IQ and slow wave activity (SWA) during non-rapid eye movement (nREM) sleep is perhaps the strongest one. In healthy adults, sleep progresses through nREM stages N1 through N3 followed by a period of REM sleep occurring roughly 60–90 min into the sleep cycle.\textsuperscript{53} Cognitive improvements in treated patients with obstructive sleep apnoea might indicate increased stability of brain activity during sleep, allowing for crucial synaptic repair and maintenance to occur, and counteracting toxic effects of arousal and hypoxic effects of obstructive sleep apnoea.\textsuperscript{33,56} This argument is concordant with findings showing that the neurochemical and gene environments of sleep and sleep activity patterns present crucial periods during which the brain can restore cellular homeostasis, amplify the signal to noise ratio, and reinforce neuronal circuitry for subsequent cognitive processing demands.\textsuperscript{38,53,54}

**Cognitive and emotional sleep**

Sleep and sleep deprivation alter molecular signalling pathways that regulate synaptic strength, plasticity-related gene expression, and protein translation in a bidirectional manner.\textsuperscript{54} Moreover, sleep deprivation can impair neuronal excitability, decrease myelination, and lead to cellular oxidative stress and misfolding of cellular proteins.\textsuperscript{53,55} Findings of an open, cross-sectional, comparative clinical trial\textsuperscript{49} suggested associations between oxidative stress markers, sleepiness, and the presence of affective symptoms in patients with sleep apnoea.
Frequent brief awakenings, and ensuing fragmented sleep, have been shown to affect cognitive and emotional functioning the next day, in a manner similar to that of total sleep deprivation. Several studies have also attempted to assess whether patients with obstructive sleep apnoea were more susceptible to sleep-loss induced performance deficits, with special emphasis on driving performance, with varied results. From a practical point of view, it is of major importance to develop reliable and practical bedside tests to help clinicians advise patients on their individual traffic accident risks. A preliminary study has provided potentially promising data for a specific EEG biomarker of neurobehavioural impairment and sleepiness. Preclinical studies suggest that sleep fragmentation independently affects brain regions similar to those affected by the intermittent hypoxia. Clinical studies of the effects of sleep deprivation on cognition in the general population suggest comparable cognitive impairments to those seen in obstructive sleep apnoea. Frequent partial arousals during sleep in patients with this disorder contribute to abnormal sleep architecture and symptoms of excessive daytime somnolence. An independent association between excessive daytime somnolence and cognitive impairment has been seen and several prospective studies have shown that excessive daytime somnolence is associated with an increased risk of cognitive decline and dementia. In a prospective cohort study, lower nocturnal oxygenation and reduction in nREM SWS sleep were associated with the development of microinfaacts and brain atrophy. Conversely, men with longer SWA sleep showed slower cognitive decline than those with shorter SWA sleep.

Cognitive sleep
The effect of obstructive sleep apnoea on sleep stages merits particular attention because each of the sleep stages, with its attendant changes in neurophysiology, is associated with facilitation of important functional learning and memory processes. In patients with obstructive sleep apnoea, the proportion of stage N2 nREM sleep has been shown to increase, whereas proportions of stages N1, N3, and REM sleep decrease. Results from experimental studies have shown specific impairments of sleep-dependent consolidation for verbal declarative information in patients with obstructive sleep apnoea. Furthermore, several clinical studies suggest disturbed spatiotemporal evolution of sleep spindles in patients with obstructive sleep apnoea during the night.

However, the effects of sleep fragmentation in patients with obstructive sleep apnoea are not easy to assess, and dynamic analysis of sleep architecture is needed to fully gauge the effect on sleep. In one study of mild obstructive sleep apnoea, in which sleep fragmentation was probably not sufficient to cause relevant decreases in SWS (eg, in N3 nREM) and REM sleep, the exponential decay function of SWA was shown as statistically significantly slower in patients compared with healthy controls. This difference was because of the more even distribution of SWA in the patients throughout the night. These results show that mild sleep fragmentation can alter the dynamics of SWA, without substantially decreasing the quantity of SWS and REM sleep, and emphasise the need to perform SWA decay analysis in sleep fragmentation disorders. In the same study, a reduction of spindle activity was seen in N2 and N3 which was not attributed to an increase of SWA. Such a reduction in total spindle density has also been reported in sleep maintenance insomnia, and is probably related to sleep fragmentation.

An integrative framework for qualitative reorganisation of memory during sleep has been suggested. The model, proposed by Landmann and colleagues, builds on studies that have shown that sleep helps with the abstraction of rules and the integration of knowledge into existing schemas during nREM SWS. REM sleep, on the other hand, benefits creativity that requires the disintegration of existing patterns. Of note, both sleep stages are generally reported as reduced or fragmented in obstructive sleep apnoea, and it is probable that some of the cognitive complaints and memory deficits described are partly acquired due to this dysregulation. In line with this argument, in one study that investigated neurocognitive deficits in obstructive sleep apnoea, the number of microarousals during the night was the best predictor of episodic memory deficit.

Traditionally, obstructive events during nREM sleep have been viewed as associated with greater cognitive deficits or impaired quality of life, whereas REM sleep events have been shown to be associated with greater sympathetic activity, hypertension, and cardiovascular instability in patients with obstructive sleep apnoea. The role of fragmented REM sleep in spatial navigational memory in patients with obstructive sleep apnoea has been addressed with a physiologically relevant stimulus. During this study, patients spent two different nights in the laboratory, during which they performed timed trials, before and after sleep, on one of two unique 3D spatial mazes. The normal consolidation of sleep was achieved with use of therapeutic CPAP throughout the first night, whereas during the second night, CPAP was only used during the REM sleep stages. Patients showed improvements in maze performance after a night of normal, uninterrupted sleep, and those improvements were substantially reduced after a night of REM disruption without changes in psychomotor vigilance. Noted cognitive improvements showed statistically significant positive correlation with the mean REM duration across both sleep conditions.

In another model, recovery of functionally inter-connected networks is proposed to occur during SWA of nREM sleep. This model stresses the importance of the appropriate spatiotemporal revolution of sleep spindles throughout nREM sleep. Sleep spindles are taken to tag those networks that have recovered sufficiently for their inclusion in the selection process during subsequent sleep. In turn, further excursions into REM sleep then
allow for safe offline reactivation, which checks and deselects fully recovered brain networks from further SWA cycles. Once the required number of SWA cycles is achieved, a presumed transition to wakefulness occurs. Regarding obstructive sleep apnoea-induced cognitive deficits, it could be argued that this model offers a robust theoretical framework for the origins of excessive daytime sleepiness and feeling unrefreshed in the morning that is reported by some patients with obstructive sleep apnoea. According to this model, this might be because of the inability to augment nREM SWA and REM sleep during the period of high waking demands. Moreover, in some patients with obstructive sleep apnoea, reduction of REM sleep can lead to dissociation of REM traits to other sleep stages, further affecting sleep windows that are crucial for memory formation and consolidation. Findings of several studies have shown that, if high homeostatic demands are not fully met during sleep, microsleeps can occur in highly active regions of the brain in the subsequent wake period. These microsleeps can lead to concomitant disability in the function associated with that region. To what extent this event takes place in patients with obstructive sleep apnoea, and whether this also contributes to attention and vigilance dysfunction and higher frequency of traffic accidents noted for this patient group, is not yet fully understood. Previously reported retarded SWA decay throughout the night in patients with even mild obstructive sleep apnoea further supports the notion of non-restorative sleep in obstructive sleep apnoea.

The degree of atrophy in the medial prefrontal cortex, an area that is associated with the generation of slow waves and one that is thought to be independently affected by obstructive sleep apnoea (figure 1), predicts the extent of impaired SWA in elderly people, and results in impaired overnight episodic hippocampal memory consolidation (figure 2A). Clinical improvement of SWA in older adults has been proposed to represent a novel treatment for mitigating cognitive decline in later life. Older adults, who express fewer prefrontal fast sleep spindles than younger adults, have shown a proportional impairment in hippocampal functioning during the subsequent wake periods, and a subsequent deficit in the ability to form new episodic memories. Fast sleep spindles represent part of a coordinated nREM sleep-dependent memory consolidation mechanism.

**Figure 2:** The proposed role for sleep in cognition and emotions

(A) Cognitive sleep: sleep apnoea and ageing have been independently associated with grey matter atrophy in the prefrontal cortex. Atrophy can mediate the degree of SWA disruption, whereas SWA in turn can mediate the degree of impaired memory retention. SWA activity disruption probably also leads to circumscribed cortical regions of increased cellular stress. (B) Emotional sleep: conceptual schematics of “the sleep to forget and sleep to remember” model are shown. Over one or several nights and many repetitions of this REMS mechanism, sleep transforms an emotional memory into a memory of an emotional event that is no longer emotional. SWA = slow wave activity. REMS = rapid eye movement sleep. Reproduced with permission and adapted from Mander and colleagues, Picchioni and colleagues, and Goldstein and colleagues.
mechanism, and hippocampal sharp-wave ripples are thought to provide feedback excitation, which initiates neuroplasticity in spindle-activated cortical neurons. Relative to slow sleep spindles, fast sleep spindle events are associated with greater hippocampal activation and greater hippocampal–cortical functional connectivity. In a study of spindle frequency changes in obstructive sleep apnoea, patients with obstructive sleep apnoea persisted in displaying a great proportion of slow spindles in frontal, central, and parietal regions during the night, unlike healthy controls, suggesting that deregulated spindle formation might be another factor contributing to cognitive complaints in patients with obstructive sleep apnoea. In another study, the sleep architecture of patients with mild obstructive sleep apnoea showed a high degree of sleep fragmentation resulting in a different time course of SWA and a decreased sleep spindle index when compared with controls. Taken together, these studies further highlight the possible role for obstructive sleep apnoea brain injury in the initiation or acceleration of cognitive decline (figure 2A) in older adults, although the exact pathophysiology of this association remains elusive.

Emotional sleep

The findings of studies that build on long-standing clinical findings of co-occurring mood and sleep disorders support a bidirectional association between sleep and the function of brain circuitry associated with emotions. Various mental health issues, such as affective disorders, emotional instability, and depression, are highly prevalent in individuals with obstructive sleep apnoea, with some studies reporting that up to 63% of individuals are affected despite substantial heterogeneity and high risk of bias. Evidence from various studies is suggestive of a role for REM sleep in selective emotional memory processing and sleep-dependent emotional memory deactivation (figure 2B). Moreover, REM sleep is suggested to play a part in recalibrating the sensitivity and specificity of the brain’s response to positive and negative emotional events. This effect probably occurs at least partly as a result of modulation of noradrenergic brain stem activity and the responsive profiles of the amygdala and medial prefrontal cortex, two regions crucial for detecting emotional salience.

Of all psychiatric disorders, the evidence for increased prevalence of obstructive sleep apnoea is particularly strong for major depressive disorder and post-traumatic stress disorder, which are both independently associated with REM sleep disturbance. Even though the causal association between these affective disorders and obstructive sleep apnoea is unclear and is probably multifactorial, the potential sleep mechanics underlying their interaction is worthy of further consideration.

Post-traumatic stress disorder is independently associated with decreases in the total time spent in REM sleep, with marked fragmentation of REM sleep suggestive of arousal-related awakenings from REM sleep linked to adrenergic surges. CPAP adherence, and therefore effectiveness, has been shown to be reduced in veterans with post-traumatic stress disorder and comorbid obstructive sleep apnoea. Based on our knowledge of sleep deficits induced by obstructive sleep apnoea, it can be argued that in patients with post-traumatic stress disorder and comorbid obstructive sleep apnoea, the additive effect of sleep disturbance can further impair the quantity and quality of REM sleep. Sleep disturbance probably affects the noradrenergic housekeeping function of REM sleep, since it has been shown that REM sleep reduces, and probably restores, concentrations of noradrenaline to baseline, allowing for optimum wakeful functioning. More specifically, several studies suggest that quiescence of activity in the locus coeruleus (a brain stem structure and a source of noradrenergic input) throughout REM sleep restores the appropriate next-day tonic–phasic response specificity (ie, appropriate adrenergic response to resting state and stimulus) within the emotional salience network (eg, locus coeruleus, amygdala, and medial prefrontal cortex). Obstructive sleep apnoea induced REM fragmentation could further aggravate the hyperadrenergic state of some patients with post-traumatic stress disorder, and lead to decreased connectivity between the prefrontal cortex and amygdala, and exaggerated amygdala reactivity. The functional outcome might be an aggravated disease course and worse prognosis. In a prospective study, higher nocturnal oxygenation during REM sleep was associated with less gliosis and neuronal loss in the locus coeruleus.

Major depression, on the other hand, is associated with exaggerated REM sleep qualities and reduced monoamine activity. The findings of several studies suggest a relationship between depression and obstructive sleep apnoea. In some patients with obstructive sleep apnoea, fragmented REM sleep can precipitate a vicious cycle of impaired regulation and rebound REM augmentation. Along with concomitant changes in neurotransmitter systems caused by hypoxaemia, this cycle might lead to further reduction in monoamine activity, increased negative rumination, and ensuing depression in genetically predisposed individuals. Through its effects on REM sleep, comorbid obstructive sleep apnoea might also lead to dysfunctional memory trace consolidation and deactivation of emotional memory from previous affective experiences. This might result in a condition of chronic anxiety within autobiographical memory networks (figure 2B). In a meta-analysis of randomised trials of treatment of obstructive sleep apnoea, a substantial improvement in depressive symptoms was reported.

Even though all theoretical constructs of a bidirectional association between sleep in obstructive sleep apnoea and psychiatric disorders discussed in this Review are indirectly supported by animal and neuroimaging
Intermittent hypoxia, neuroinflammation, and ischaemic conditioning

The cognitive and emotional effects of obstructive sleep apnoea are equally attributable to oxidative and neuroinflammatory effects on the emotional salience network. In obstructive sleep apnoea, repetitive occlusions of the upper airway lead to intermittent hypoxia and recurrent hypoxaemia, typically characterised by short cycles of hypoxia and reoxygenation. However, the patterns vary greatly between patients and, depending on the idiosyncratic characteristics of each individual, the end results might be either adaptive or maladaptive. The outcome will also depend on the dynamic interplay between the specific type, amount, duration, and frequency of reactive oxygen and nitrogen species produced, the intracerebral localisation, and the microenvironmental antioxidant activity. Additional interplay depends on factors such as genetic makeup, nutrition, and other lifestyle-related variables, all of which affect the redox status. Various studies suggest that the severity of hypoxia, its duration, and cycle frequency, are fundamental determinants of outcomes (figure 3A). For example, short, mild, and lower cycle frequency is generally acknowledged to generate beneficial and adaptive responses in the brain, such as ischaemic preconditioning. Conversely, chronic, moderate to severe, and high frequency intermittent hypoxia can induce maladaptive disruption of homeostatic mechanisms, leading to dysfunction and sterile neuroinflammation (ie, inflammation not caused by the infective agent).

Ischaemic preconditioning represents a generalised adaptation to ischaemia by various cells. In obstructive sleep apnoea, induction of ischaemic preconditioning is thought to be caused by the activation of several gene programmes, including hypoxia inducible factor-1, vascular endothelial growth factor, erythropoietin, atrial natriuretic peptide, and brain-derived neurotrophic factor. Various end mechanisms and pathways play a part, including those of long-term facilitation of phrenic motor output, chemoreflex activation, vascular remodelling, neo-angiogenesis, productive autophagy, reactive gliosis, various synaptic changes, and modulation of adult hippocampal neurogenesis (figure 4). CPAP treatment of obstructive sleep apnoea partly reverses the damage in hippocampal regions, and ameliorates some of the associated cognitive deficits, possibly by modulating adult neurogenesis. In a neuroimaging study, co-existing of hypothropic and hypertrophic changes in the brains of patients with obstructive sleep apnoea was taken to show the evolving nature of obstructive sleep apnoea-associated brain injury. Persisting maladaptive neuroinflammatory processes are proposed to exist alongside adaptive mechanisms of increased brain plasticity and ischaemic preconditioning. In a study that compared the cognitive performance of patients with high and low levels of hypoxaemia, an unexpected benefit of higher hypoxaemia on memory was shown in a carefully matched clinical cohort, after controlling for demographic factors and other aspects of obstructive sleep apnoea severity.

Another powerful central neuroprotective adaptive mechanism for ischaemic events has been shown following the activation of the intrinsic neurons of the cerebellar fastigial nucleus. Neurostimulation of these nuclei seems to provide protective reduced excitability of cortical neurons during subsequent ischaemic episodes, and leads to reduced immunoreactivity of cerebral microvessels. The compensatory entraining of the cerebellum by hypertrophic hippocampi has been proposed to occur in some young patients with mild obstructive sleep apnoea. 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 and novel conditions, and for associative learning. Failed adaptation of cerebellar networks in response to injury led to cognitive deficits and hyperactivity, distractibility, ruminative behaviours, dysphoria, and depression in some patients. Several studies of sleep, their true mechanisms are probably more complex.
Neurogenesis. Θ Hippocampal is thought to modulate the functional properties of the cerebellum and to govern hippocampal which runs from the dentate gyrus, to Θ Theta (θ) is the archetypical rhythmic activity in the hippocampus (structure shown here in rainbow colours), with sleep apnoea.

Figure: Putative theoretical neuromechanisms behind plastic changes noted in clinical studies of patients with sleep apnoea

Thermal (θ) is the archetypical rhythmic activity in the hippocampus (structure shown here in rainbow colours), which runs from the dentate gyrus, to CA3/CA1 of the hippocampus, and finally to the entorhinal cortex. Hippocampal θ is thought to modulate the functional properties of the cerebellum and to govern hippocampal neurogenesis. A decrease in θ band occurs after apnoea and hypopnoea events in some patients with sleep apnoea. CPAP normalises these EEG changes. Hypofunctioning fornix (signified here by red dotted line) likely alters neurogenesis in the dentate gyrus and possibly contributes to mild cognitive decline in obstructive sleep apnoea. CPAP= continuous positive airway pressure. EEG=electroencephalography. Reproduced with permission from Rosenzweig and colleagues.

Search strategy and selection criteria
We identified references for this Review by searches of PubMed between 2002 and 2015, and references from relevant articles. Additionally, several seminal historic references were added. We used the search terms “sleep apnoea/apnea”, “intermittent hypoxia”, “sleep”, “sleep deprivation/fragmentation”, “sleep disordered breathing”, and “dementia”, “mental health/emotions”, “Alzheimer’s disease”, “brain structure”, “cognitive decline”, “cognitive function”, or “cognition”. Articles were restricted to those available in English. We made the final selection by using the most relevant articles.

Dynamic changes in transcription of inflammatory genes have been shown after exposure to intermittent hypoxia, with expression of most inflammatory markers increasing over time. Increased concentrations of prostaglandin E2 in neural tissue have been noted in hippocampal and cortical regions accompanied by lipid peroxidation of polyunsaturated fatty acids. Increased carboxylation and nitrosoylation-induced oxidative injury have been shown to emerge in susceptible brain regions and promote increased excessive daytime somnolence. Toll-like receptor 4 (TLR4) expression and activity is increased on monocytes of patients with obstructive sleep apnoea, and ligands for TLR4 are increased in the serum of children with obstructive sleep apnoea. The microglia of the cortex and brainstem show TLR4 expression after chronic intermittent hypoxia, which is postulated to have a region specific and differential (adaptive or maladaptive) role. This finding is of particular interest since TLR4 has also been strongly implicated in several inflammatory and neurodegenerative disorders, including vascular dementia and Alzheimer’s disease. In cognitively healthy adults, intermittent hypoxia has been associated with increases in phosphorylated and total tau and amyloid β concentrations in cerebral spinal fluid. Cerebral amyloidogenesis and tau phosphorylation, key components of Alzheimer’s pathology, along with neuronal degeneration and axonal dysfunction, have been shown in cortex and brainstems of animals exposed to intermittent hypoxia. These findings support a role for neuroinflammatory processes in cognitive and emotional deficits of patients with obstructive sleep apnoea. They further suggest a close association between hypoaxemia induced maladaptive processes and dementia (figure 3C).
Conclusions and future directions

Disruption of sleep physiology by obstructive sleep apnoea is an underappreciated factor, which, together with hypoxaemia and other already recognised factors, might further aggravate age-related memory deficits.2,3,6,7,8 Clinically, this dynamic interplay also underscores many subjective and objective cognitive and emotional complaints in some patients.2,7,9 An understanding of the proportional effect of these factors is a major challenge because they occur simultaneously, probably target similar neurocircuitry, and probably share the same end-stage adaptive and maladaptive cellular mechanisms.3,5 Persistent deficits, even after long-term treatment with CPAP in some patients, suggest that early detection of the CNS sequelae in obstructive sleep apnoea is essential so that appropriate treatment is given before irreversible atrophic and metabolic changes occur. However, the timing and the duration of treatment, and optimum treatment population, are still unclear and should be addressed in future prospective randomised control studies.

Studies discussed in this Review strongly suggest that tapping into the therapeutic potential of ischaemic preconditioning, while working on ameliorating the acute and chronic effects of neuroinflammation, could offer legitimate new therapeutic targets in obstructive sleep apnoea.13,14,16,78 Although in their infancy, studies of clinical approaches that target the sleep disturbance arm of this intricate equation advocate substantial potential future treatment interventions.14,15,17

In conclusion, findings raise valid questions about the mechanics of associations between obstructive sleep apnoea, various cognitive and emotional deficits, and dementia, and further highlight the public-health importance of detecting and targeting those at highest risk for cognitive decline.

Contributors
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Declaration of interests
We declare no competing interests.

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