Title: Cognitive deficits in obstructive sleep apnea: insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation

Authors: Michelle Olaithe^{1,2}, Romola S. Bucks¹, David R. Hillman², Peter R. Eastwood²

Affiliations:

1. School of Psychological Science, University of Western Australia, Perth, Australia
2. Centre for Sleep Science, School of Anatomy, Physiology and Human Biology, Perth, Australia

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Correspondence:

Michelle Olaithe

School of Psychological Science
The University of Western Australia
35 Stirling Highway
Crawley 6009, Western Australia

Email: michelle.olaithe@research.uwa.edu.au

SUMMARY

Obstructive sleep apnea (OSA) is a nocturnal breathing disorder that is associated with cognitive impairment. The primary determinants of cognitive deficits in OSA are thought to be sleep disruption and blood gas abnormalities. Cognitive impairment is also seen in other disorders that are characterised primarily by sleep disturbance (e.g., sleep restriction/deprivation, insomnia) or hypoxia/hypercarbia (e.g. chronic obstructive pulmonary disease (COPD)). Assessment of the cognitive defects observed in these other disorders could help better define the mechanisms underlying cognitive deficits in OSA. This study utilised meta-review methodology to examine the findings from systematic reviews and meta-analyses of the effects of untreated OSA, COPD, insomnia and sleep deprivation on cognitive function in adults, compared with norms or controls. Eighteen papers met inclusion criteria: 7 in OSA, 2 in insomnia, 5 in COPD, and 4 in sleep deprivation. OSA and COPD were both accompanied by deficits in attention, memory, executive function, psychomotor function and language abilities, suggesting that hypoxia/hypercarbia may be an important determinant of deficits in these domains in OSA. Both OSA and sleep deprivation studies were accompanied by deficits in attention and memory, suggesting that short-term sleep disturbance in OSA may contribute to deficits in these domains. Visuospatial deficits were unique to OSA, suggesting the contribution of a mechanism other than sleep disturbance and hypoxia/hypercarbia to this problem. Our findings suggest that the cognitive deficits associated with untreated OSA are multidimensional, with different physiological disturbances responsible for differing cognitive problems.

Keywords: Obstructive sleep apnea; neuropsychological function; mechanisms-of-harm; sleep disruption; hypoxia; cognition; meta-review

GLOSSARY

AI

Arousal index

COPD

Chronic obstructive pulmonary disease

EEG

Electroencephalogram

ERP

Event related potentials

IAD

Integrated area of desaturation

OSA

Obstructive sleep apnea

SDB

Sleep disordered breathing

SEM

Structural equation modelling

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterised by repetitive episodes of partial (hypopneas) or complete (apnea) obstruction of the pharyngeal airway. Varying degrees of hypoxia and hypercarbia accompany these events, which are usually terminated by brief arousals from sleep. The repetitive nature of apneas and hypopneas results in fragmented sleep and disturbed sleep architecture. OSA is estimated to occur in 9% of middle-aged women, and 27% of middle-aged men (1), and these figures are rising with population ageing and weight gain (2), with projected costs of \$US3.4-6.9B per annum (3), two- to three-fold increased risk of motor vehicle accidents (4), mood disruption, occupational injuries and absenteeism, and greater risk of relationship discord, reduced quality of life (5), and impaired cognition (6).

The profile of cognitive deficits in OSA has been summarised in several systematic reviews and meta-analyses (7-11) with a recent meta-review of these studies concluding that individuals with OSA exhibit deficits in the cognitive domains of attention/vigilance, delayed long-term visual and verbal memory, visuospatial/constructional abilities, and executive functions. Language ability and psychomotor function appear to be spared (6).

While the profile of cognitive deficits in OSA is becoming clearer, the underlying mechanisms that impair cognition in OSA remain uncertain. The dominant theoretical framework of cognitive harm focuses on hypoxia, hypercarbia, and sleep disruption (12, 13). However, evidence for these mechanisms remains equivocal (14). For example, in the most thorough review of relationships between indices of nocturnal symptoms and cognitive deficits in OSA, to date, Aloia et al. (14) found no consistent relationship between degree of cognitive impairment reported and the severity of sleep disturbance or hypoxia.

1 It is likely that some of the ambiguity in these relationships stems from difficulty in
2 separating the contribution of sleep disturbance and blood gas abnormalities, as these events
3 often co-occur in OSA. To date, just one study (15) has used a statistical approach to separate
4 the relative impact of hypoxia and sleep disruption on cognition in OSA, and none have
5 considered hypercarbia separately. Olaithe et al. (15) applied structural equation modelling
6 (SEM) to partition hypoxia from sleep disruption, and used this model to examine the
7 relationship between these mechanisms of harm and cognitive deficits in an OSA sample.
8 They found that sleep fragmentation, but not hypoxia, was associated with deficits in
9 attention and executive function. However, due to the co-occurrence of apneas/hypopneas
10 (hypoxic events) and arousals (sleep disrupting events), and the use of traditional measures of
11 respiratory and sleep disturbances, which count the number of events, this statistical model
12 maintained a high degree of association between sleep disruption and hypoxic events ($r =$
13 .70). As such, this statistical approach was unable completely to separate effects of hypoxia
14 from sleep disruption using traditional indices of nocturnal symptoms.
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17 An alternative approach is to compare OSA with conditions where just one of the proposed
18 mechanisms of harm predominates, using meta-review. There is marked heterogeneity in the
19 measures used to quantify disturbances of cognition, sleep and blood gas indices, and studies
20 have often involved relatively small sample sizes. Meta-review of meta-analytic and/or
21 systematic reviews represents one way to address this ambiguity in both mechanism and
22 measurement, by aggregating performance across many tasks, indices, participant numbers
23 (16), and conditions.
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26 Better to understand the mechanisms of cognitive deficits in OSA, we used meta-review
27 techniques to compare the cognitive profiles of disorders that differentially disturb sleep
28 architecture, and/or cause hypoxia and hypercarbia. Such an approach allows the overlapping
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influences of blood gas disturbances and sleep disruption seen in OSA to be teased apart.

Identification of shared or unique cognitive deficits occurring between OSA and exemplar disorders may shed light on the underlying mechanisms of cognitive harm in OSA. Aspects of such a comparative, disease-based approach have been used in three previous studies. In 1995, Roher et al. (17) compared the cognitive function of individuals with OSA and chronic obstructive pulmonary disease (COPD), positing that because airflow limitation was a key component of both conditions any differences between the groups could be attributed to sleep disruption. The study reported that individuals with OSA were more impaired than those with COPD on sustained attention tasks. In 2001, Fulda and Shulz (18) examined differences in cognition between individuals with OSA and those with insomnia, demonstrating that individuals with OSA exhibit greater cognitive deficits than those with insomnia on tasks assessing driving ability and attention. Finally, in 2015, a narrative review by Andreou et al. (19) reported many similarities in the cognitive profiles of COPD and OSA, leading the authors to conclude that the underlying mechanisms of cognitive harm were similar.

The present study extends these earlier investigations by defining and comparing the effects of OSA (characterised by hypoxia, hypercarbia, short- and chronic sleep disruption), COPD (characterised by hypoxia and hypercarbia), insomnia (characterised by chronic sleep disruption) and experimental studies of sleep deprivation (characterised by short-term sleep disruption) on cognition. COPD and OSA represent two of the most common respiratory conditions. Both increase in prevalence with age, are characterised by airflow limitation, and are accompanied by hypoxia and hypercarbia (1, 20). In contrast to COPD, but similarly to OSA, individuals with insomnia and those who are exposed to sleep deprivation, experience systematic sleep disturbance. For the purpose of this study, individuals with insomnia were considered to exhibit chronic sleep disturbance (diagnostic criteria is non-restorative sleep for ≥ 1 month) (21), while participants in experimental sleep deprivation studies are generally

exposed to short-term sleep loss (e.g. ≤ 48 hours). The differentiation between chronic and short-term sleep disturbance is important, as it is likely that there are different cognitive consequences (22). Comparing and contrasting the cognitive profile of OSA with those of COPD, chronic insomnia, and short-term sleep deprivation (summarised in Table 1) could provide useful insights into the relative contributions of chronic and short-term sleep disturbance, and hypoxia/hypercarbia to the cognitive deficits observed in OSA.

METHOD

Search

All review papers addressing the topic of cognitive function in OSA, COPD, insomnia, and sleep deprivation between 1st January 1980 and 12th January 2016 were examined. Systematic reviews and meta-analyses were included if they examined one or more of these conditions in adults and compared data with norms or controls before any treatment or intervention. Figure 1 presents a summary of the search terms selected, databases searched and numbers of papers included and excluded at each stage of the selection process.

Reasons for exclusion

Papers were excluded if they examined a special population (e.g., OSA in individuals with traumatic brain injury), did not examine cognition, examined cognition after treatment but not before, examined subjective cognitive complaints without objective measures of cognition, undertook a review that was not systematic, if the search method was unclear such that it could not be determined if the review was systematic, if the paper was not a review, examined a paediatric population, did not examine OSA or COPD or insomnia or sleep deprivation, was not written in English, and/or did not study humans.

Division of cognitive domains

Broadly, cognitive function can be divided into the domains of attention, memory, executive function, visuospatial/constructional abilities, psychomotor ability, and language function.

Table 2 presents a definition of each domain, its neural correlates and subdomains, an example activity, and an assessment task for each domain or subdomain.

Several previous reviews have reported a ‘general cognition’ domain, therefore we have included this in the present analyses. A full explanation of domains, subdomains of each domain, and assessments is beyond the scope of this paper, however excellent resources include those by Schoenberg & Scott (23), Strauss, Sherman & Spreen (24), and Lezak, Howieson & Loring (25).

The present analysis used the classification of neuropsychological tasks provided in each paper, which were, for the most part, the same. There were, however, some discrepancies, most notably in relation to tasks with multiple components. For example, the Trails task has two components, Trails A and Trails B. Trails A is widely regarded to assess attention, while Trails B is thought to assess executive functions. Some papers summed these two components into one Trails score and reported it to assess attention.

Differences in the way tasks are classified is also an issue for the wider neuropsychological literature making choice of tasks confusing. Even across the above neuropsychological references provided (22, 23, 24) there are differences in the way tasks are classified. Some of this discrepancy may be because of: the way tasks are broken down; the model of cognition used to define tasks and domains of cognition; and inadvertent measurement of multiple domains of cognition by the task, a common dilemma. To aid task choice, we have provided a set of example tasks we consider to adequately assess the underlying domain.

Data extraction

The search strategy resulted in 7 papers summarising cognitive function in OSA, 5 in COPD, 2 in insomnia, and 4 in sleep deprivation. Basic descriptive details of these papers are presented in text in Table 3, and further details are provided in the Online Supplementary Appendix (Tables 1-4).

Two papers (8, 9), analysing cognition in OSA, provided separate meta-analyses of; 1) normative and, 2) control papers. In the case of Wallace & Bucks (9) we report only the effect sizes of the control data. We do not report the normative data, as control data were included in the analyses. For the Beebe et al. (8) paper, we report all control data, and a subset of the normative data, that did not include control data: Global cognition, and Visual memory.

The pooled effects, summarised across review papers, for a given domain or subdomain were marked as ‘YES’ if there was evidence of deficits in a cognitive domain compared with norms or controls, and as ‘NO’ if there was no evidence of cognitive deficits, or the summarised score across reviews, was inconclusive.

Effect sizes (Cohen’s d) were extracted from meta-analyses, for which a mean effect size ($\Sigma d/n$) was calculated for each domain within a study (controlling for multiple outcomes per domain), and then averaged across studies. The absolute value of the effect sizes was used in the present paper. Effect sizes of $d \geq 0.20$ were considered small, $d \geq 0.50$ medium, $d \geq 0.80$ large and $d \geq 1.00$ very large (26).

A set of rules was developed to determine whether cognitive deficits were present for any given condition. First, there needed to be a majority of systematic review papers for which a deficit was reported. Second, if an equal number of studies reported deficits to those reporting

an absence of deficits we then referred to the available meta-analytic effects. If there were at least 2 meta-analytic studies, and the average effect was at least of medium size (≥ 0.5), we concluded that a cognitive deficit was present for that domain. Otherwise, we concluded that there was no deficit.

RESULTS

Cognitive deficits in OSA

The search found two new papers reporting on cognition in adults before OSA treatment (27, 28) to add to the 5 papers (7-11) reported in our 2012 meta-review on cognition in OSA (6) (see Online Supplement: Table 1). Inclusion of these two recent reviews into the current meta-review produced results consistent with the previous meta-review, which demonstrated that individuals with OSA had deficits in the domains of attention, executive function, visuospatial/constructional function, and in the subdomains of verbal immediate memory, delayed long-term memory, and visual delayed long term memory. Their inclusion also resulted in deficits being found in language function and psychomotor function. Small to large effects were evident for most studies, across most domains (Table 4).

Cognitive deficits in COPD

Five systematic reviews (29-33), but no meta-analyses, examining cognition in adults before treatment for COPD met the inclusion criteria (Online Supplement: Table 2). Individuals with COPD demonstrated deficits in attention, memory, executive function, psychomotor function, visuospatial/constructional abilities, and language. General cognition, by comparison, was

preserved and working memory was unexplored. As there were no meta-analyses of cognitive deficits in COPD, no effect sizes are reported.

Cognitive deficits in insomnia

One meta-analysis (34) and one systematic review (18) examining cognition in adults before treatment in insomnia met the inclusion criteria (Online Supplement: Table 3). The majority of papers reported no deficits in attention, memory, executive function, psychomotor function, visuospatial/constructional function, language function, or general cognition. The systematic review by Fulda and Schulz (18) suggested that insomnia impairs working memory, however, this domain was not examined in the meta-analysis by Fortier-Brochu et al. (34). As such, it was defined as not impaired due to insufficient evidence.

Cognitive deficits in sleep deprivation

Three meta-analyses (22, 35, 36) and one systematic review (37) examining cognition in adults with sleep deprivation met the inclusion criteria (Online Supplement: Table 4). Individuals exposed to sleep deprivation demonstrated deficits in attention, memory, and general cognition. Small to very large effects were noted across most affected domains, across most studies. Results for psychomotor function were equivocal, as only one meta-analysis provided an effect size. As for insomnia, no negative effects were recorded for this domain. Visuospatial/constructional abilities were not explored in any of the reviews summarised.

Comparison of cognitive profiles between conditions/disturbances

A summary of the cognitive profiles found in systematic reviews or meta-analyses in OSA, COPD, insomnia and sleep deprivation is provided in Table 5.

Deficits in attention and memory. OSA, COPD, and sleep deprivation are all accompanied by deficits in attention and memory. This suggests that short-term sleep disruption (shared in OSA and sleep deprivation) and/or hypoxia/hypercarbia (shared in OSA and COPD) contribute to attention and memory deficits in OSA.

Deficits in executive function, psychomotor function and language. OSA and COPD are both accompanied by deficits in executive function, psychomotor function and language ability. However, deficits in these domains were not seen in either sleep deprivation or insomnia. These findings suggest that hypoxia/hypercarbia, rather than sleep disruption, contributes to cognitive deficits in executive function, psychomotor function and language ability in OSA.

Deficits in visuospatial/constructional ability. Deficits in visuospatial/constructional function were unique to OSA. This may suggest another, as yet, undefined contributing factor.

General cognition and working memory. Neither OSA, COPD, nor insomnia was accompanied by deficits in the domains of general cognition or working memory. This suggests that these domains are relatively unaffected by hypoxia/hypercarbia or sleep deprivation.

DISCUSSION

The present paper used meta-review methodology to compare the cognitive profiles of individuals with OSA, COPD, insomnia, and those exposed to experimental sleep deprivation. Cognitive deficits were observed in OSA (attention, memory, executive function, psychomotor function, visuospatial/construction function and language function), COPD (attention, memory, executive function, psychomotor function, language function), and sleep deprivation (attention, memory, and general cognition), but not in individuals with insomnia.

These findings suggest that hypoxia/hypercarbia (present in OSA and COPD) is consistently associated with impairments in attention, memory, executive functions, psychomotor functions and language ability, whilst short-term sleep disturbance (present in sleep deprivation studies and OSA) but not chronic sleep disturbance (present in insomnia and OSA) appears to play a role in impaired attention and memory across these disorders/disruptions. Finally, visuospatial deficits were unique to OSA, suggesting another mechanism may be responsible.

Comparing the present findings to past literature

Fulda and Schulz (18) used a systematic review of 56 papers to define the cognitive profiles of individuals with sleep disordered breathing (SDB), insomnia, and narcolepsy. Their review showed that people with SDB exhibited more pronounced behavioural and cognitive impairment than individuals with insomnia across driving ability, and tasks assessing attention. Similar to Fulda and Schulz (16), the present review found disparity in cognitive profiles between individuals with insomnia and OSA, finding that the latter were more impaired than those with insomnia in attention, memory, executive function, psychomotor function, visuospatial/construction function, and language function.

In a narrative-review characterising and comparing neuropsychological performance in individuals with COPD and OSAS, Andreou et al. (19) noted similar profiles of cognitive deficit between the two conditions. Specifically, they noted deficits in attention, psychomotor speed, memory and learning, visuospatial and constructional abilities, executive functions, and language skills. Similar cognitive profiles were seen in the COPD and OSA groups in the present review, suggesting a common mechanism-of-harm, namely hypoxia/hypercarbia.

Interestingly, the present review did not find decrements in visuospatial/constructional abilities for individuals with COPD. This disparity may be due to the narrative nature of

Andreou et al.'s review (19), which is in contrast to our exclusion of narrative reviews due to a lack of clarity regarding search and selection criteria.

Psychomotor function in OSA. Aloia et al. (14) investigated the relationship between the degree of cognitive deficits, and the severity of sleep disruption, and hypoxia/hypercarbia.

Their review largely found no association between hypoxia, sleep disruption and cognition.

However, while there was no association between sleep indices and cognition in the domain of psychomotor function, two papers explored fine motor co-ordination, a subdomain of psychomotor function, using pegboard tasks, and demonstrated impairment associated with the level of hypoxia/hypercarbia, but not sleep disruption. Furthermore, this domain did not improve with treatment, suggesting irreversible damage. The present paper also found that psychomotor function is impaired in OSA and COPD, supporting a critical role for hypoxia/hypercarbia in impairing speeded motor skills. These findings suggest that psychomotor function is an important area for further examination in individuals with OSA.

Neuroimaging in OSA. Zimmerman and Aloia (38) reviewed 17 papers examining neuroimaging in OSA. Their review found evidence for hippocampal atrophy (the hippocampus being a neural substrate supportive of memory function), and neurochemical data suggestive of white matter impairment in the frontal lobes (white matter tracts are important for speedy and efficient neural transmission), plus a lack of activation in the dorsolateral prefrontal cortices (associated with executive functions). Further differences in neural function were found in individuals with OSA in cortices involved in motor, sensory, and autonomic activity. These areas of structural brain damage are consistent with the behavioural findings of the current meta-review which showed deficits in executive, memory, and psychomotor functions in OSA.

1 Event related potentials (ERP), in particular P3 latency, measure an individuals' reaction to a
2 stimulus, and are related to brain activity associated with early attention to, and processing of,
3 novel stimuli. A review by Raggi and Ferri (41) examining ERPs in OSA found increased P3
4 latency for visual and auditory stimuli, suggesting that individuals with OSA exhibit
5 particular problems with speed of processing and processing novel stimuli. These data are
6 consistent with the findings of the present paper, which also found deficits in attention and
7 executive functions (processing novelty), and auditory and visual stimuli (immediate and
8 delayed verbal memory, and delayed visual memory).
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10 Most previous reviews have noted the variability in cognitive profiles that are reported across
11 published studies (18, 19, 38, 39). Two key issues have been highlighted in these reviews.
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13 Firstly, that inter-individual differences, which may affect the expression of cognitive
14 dysfunction, were generally unaccounted for in the papers. To clarify the cognitive profile of
15 OSA future research needs to consider and report inter-individual variables including; gender,
16 age, intelligence, cognitive reserve, education, length of illness, comorbidity, range of disease
17 severity, obesity, and individual vulnerability to sleep deprivation. Secondly, that many
18 papers did not explore the association between cognitive deficit and indices of harm,
19 suggesting that future studies should examine the relationship between multiple sleep
20 parameters and cognitive deficit.
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22 *Future directions*

23 The present study aimed to explore the potential roles of hypoxia/hypercarbia and sleep
24 disturbance to cognitive deficits in OSA. In pursuing this objective, several observations were
25 made that provide a basis for possible areas for future research: 1) there are important
26 differences in the cognitive effects of short-term (sleep deprivation) and chronic (insomnia)
27 sleep disruption, 2) individuals with insomnia may not universally experience objective sleep
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loss, 3) assessing cognition across a domain may miss information available from examination of its subdomains, 4) OSA comorbidities can be important in the aetiology of cognitive deficits, and, 5) the importance of considering mechanisms of harm in evaluation of these deficits. These ideas are expanded below:

1) Chronicity of sleep disruption. Short-term sleep disruption may be particularly deleterious for cognition across a wide range of capacities. Pilcher and Huffcut (22), reported in the results, explicitly examined the difference between partial, short-term, and chronic sleep deprivation, and reported that partial sleep deprivation resulted in poorer cognition than short-term or chronic sleep deprivation. They surmised that partial sleep deprivation may act more like sleep fragmentation in the way it affects psychology, physiology and chronobiology, but reported a dearth of research comparing the deleterious effects of sleep fragmentation and partial sleep deprivation and, as such, were unable to expand on this notion.

The relative importance of acute sleep deprivation in a chronic disease such as OSA is unclear, especially given that in many chronic diseases there may be some degree of adaptation (40). It is currently unknown whether individuals with OSA experience long-term sleep disturbance alone, or whether (due to the night-to-night variability in disease expression), they experience a combination of short- and long-term sleep disturbance. It is well established that the severity of an individual's sleep apnoea will change, if they shift positions (41), from night-to-night (42), and depending on whether the individual is at home or in a clinic, with differences in sleeping environment and degree of comfort and familiarity with it. It is reasonable to expect that such changes will also result in a variable degree of short and long-term sleep disruption. Regardless of the mechanism, our analyses suggest that short-term sleep deprivation plays a critical role in cognitive dysfunction in OSA, and to a

greater degree than long-term sleep disruption. Indeed, it may be the very acute, but changeable nature, of this disruption that is critical.

Furthermore, it is probable that age-related differences were present between the OSA and sleep deprivation participants, however, as the sleep deprivation papers did not report mean ages this is not certain. While differences in age between OSA and sleep deprivation studies might be expected to affect the cognitive profile observed, our analysis shows more similarities in cognitive profile between OSA and sleep deprivation studies (short term sleep disruption), than similarities in cognitive profiles between OSA and insomnia (long-term sleep disruption). Our analysis suggests that for the domains of attention and memory, short-term sleep disruption causes cognitive problems that are separate from cognitive problems associated with longevity.

Ultimately, the way different types of sleep disruption interfere with cognition requires further investigation. Ideally, this review would have included data from sleep fragmentation as well as deprivation studies, but no systematic reviews or meta-analyses of the sleep fragmentation literature meeting the selection criteria were found.

2) *Objective or subjective sleep loss in insomnia.* Differences in the perception of sleep disruption could underlie the relative preservation of cognitive function in insomnia compared with OSA, COPD, and sleep deprivation. For instance, there is debate over whether individuals with insomnia universally experience objective sleep disruption, or whether the disorder is characterised by the subjective experience of sleep disruption (43). A neurocognitive model of insomnia proposes that insomnia leads to conditioned cortical arousal, evidenced by a high proportion of high-frequency EEG activity during sleep (44). High frequency EEG, present in insomnia, is associated with a number of cognitive activities including conscious perception and memory formation. High frequency EEG may, therefore,

underlie cerebral activity that allows a misperception of one's sleep or wake state (44).

Ultimately, insomnia may be a poor model of chronic sleep disruption, and other diseases or conditions, for example chronic pain, may provide a better model.

3) *Fractionation of cognitive domains.* Many subdomains of cognition were unexaminable as there were few or no data; this was particularly true for papers examining sleep deprivation. Further studies that fractionate domains into subdomains may reveal more distinct patterns of cognitive damage in each sleep disorder. In support of this, where domains were divided into subdomains, not all subdomains were impaired (9). Separation of domains must be based on neuropsychological theory, with suitable neuropsychological tasks measuring each subdomain. For assistance with this we commend the papers of Lezak, Howieson (25), Strauss, Sherman (24), and Schoenberg and Scott (23), and we have provided an example task with good measurement properties for each sub-domain in Table 1 of this paper.

4) *Comorbidities.* Insomnia is frequently comorbid with other sleep disorders, particularly OSA (45), mood disorders (46), and other chronic medical conditions (47). These comorbidities could interact to produce confounding results in the cognitive profile reported. That said, if the insomnia samples reviewed had a higher than usual prevalence of OSA, we might have anticipated a consistent pattern of findings between insomnia and OSA. Such consistency was not found.

Comorbidities are also emerging as a crucial factor in cognitive harm in OSA (48). It is possible that, without comorbidity, OSA does not impact on cognition. Indeed, several studies suggest that cognitive deficit in OSA is the result of multiple insults to brain function (15, 48), and that hypoxia/hypercarbia and sleep disruption are insufficient in themselves. Indeed, comorbidities affecting cognition in OSA could account for the similarities in

cognitive deficits seen in COPD, as patients with COPD are likely to have these same comorbidities (e.g., overweight, and hypertension) (25).

5) *Measurement of mechanisms of harm.* The frontal lobe hypothesis suggests that sleep disruption combined with blood gas abnormalities creates cellular injury and interruptions to the normal restorative processes of sleep, leading to impaired functioning of the prefrontal cortices and, ultimately, executive deficits (12, 13). The evidence presented here suggests that hypoxia/hypercarbia alone is sufficient to lead to executive deficits, but also impacts on attention and memory, albeit the available evidence does not allow us to consider the joint or separable impact of hypoxia and/or hypercarbia. By contrast, short-term sleep disruption appears to impact on attention and memory only.

To clarify our understanding of the nature of the relationship between indices of nocturnal symptoms and cognitive deficits, measures are needed that do not rely on ‘counts’ of events. For example, the arousal index (AI), a traditional marker of sleep disruption, counts the number of times arousals occur per hour of sleep. These arousals often co-occur with apnoeic events as they are involved in terminating the event and restoring breathing. Instead, measures are needed that capture individual differences in depth and time spent in a hypoxic state (e.g., the Integrated area of desaturation (IAD)(49)), and the minutiae of sleep fragmentation (e.g., spectral analysis).

Furthermore, whilst reviewing the literature, we noted that while hypercarbia is routinely examined in COPD, there is a distinct lack of examination of the relationship between hypercarbia and cognitive deficits in OSA. Authors are beginning to communicate the importance of examining hypercarbia when investigating cognitive deficit in OSA (50). In support of this examination, some papers have demonstrated greater association between hypercarbia, than hypoxia, and cognitive deficit (51, 52), and demonstrated that hypercarbia

and hypoxia may affect different neurocognitive domains (53) Further examination may be made possible with better instrumentation, and if hypercarbia data were routinely collected at over-night sleep-studies.

Completeness of review

The present review aimed to gather as many review and meta-analytic studies examining cognition in OSA, COPD, insomnia, and sleep deprivation as possible. As such, a wide set of databases was searched, using a range of terms, and this returned many relevant papers. In order to select the most relevant papers we used stringent inclusion criteria. Furthermore, due to the novelty of this approach, we chose to make conservative judgements about the presence or absence of deficits.

Despite much relevant literature, not every cognitive domain was examined to the same extent in each condition/ disturbance by the included reviews. Attention seemed most exhaustively examined in insomnia, memory in OSA, and executive functions across all conditions/disturbances.

Conclusions

The present paper systematically analyses the overlaps in, and distinctions between, the cognitive profiles of people with OSA, insomnia, COPD, and sleep deprivation. This was undertaken to examine the basis for cognitive deficits in OSA including the potentially separable contributions of hypoxia/hypercarbia and sleep fragmentation, and to provide stimulus for future research.

Cognitive deficits shared by OSA and COPD (attention, memory, executive function, psychomotor function and language abilities) suggest a core role for hypoxia and/or

hypercarbia. Cognitive deficits shared by OSA and sleep deprivation (attention and memory) suggest a central role for sleep disturbance. As visuospatial deficits were unique to OSA, this suggests a mechanism not identified in the present review, for which other neurohumoral influences of OSA, including autonomic and endocrine disturbances, may be relevant. The lack of shared cognitive deficits between OSA and insomnia may indicate that the chronic sleep loss component of OSA does not drive the cognitive deficits associated with it. Alternatively, insomnia may be a poor exemplar of chronic sleep disruption experienced in OSA.

These findings are consistent with and extend the findings from other analyses, providing evidence for the crucial, and somewhat separable roles of sleep disruption and blood-gas abnormalities in the pathogenesis of cognitive deficits in OSA.

Practice points

- Clarifying mechanisms of harm in OSA will enable greater understanding of which patients are at greatest risk of cognitive deficit, and enable better clinical care and treatment.
- Findings demonstrate widespread cognitive deficits in OSA, COPD, some deficits in short-term sleep deprivation, and comparatively intact cognition in insomnia.
- In OSA, short-term sleep disturbance appears to contribute to deficits in attention and memory, and hypoxia/hypercarbia appears to affect attention, memory, executive function, psychomotor function, and language abilities, whilst the mechanism affecting visuospatial abilities requires further investigation.

Research agenda

Further elucidation of the mechanisms of harm in OSA will be enabled by:

- Better measurement and reporting of multiple sleep parameters, such as hypoxia, hypercarbia, short- and chronic sleep disruption;
- Indices of hypoxia that capture individual differences (for example the IAD), or indices of sleep fragmentation that do not rely on subjective classification of arousals (for example spectral analysis), may demonstrate better association with cognitive deficit;
- Routine measurement and reporting of hypercarbia at over-night sleep studies;
- Breaking broad cognitive domains into more specific subdomains;
- Consideration and reporting of inter-individual variables including gender, age, intelligence, education, length of illness, comorbidity, range of disease severity, obesity, individual vulnerability to sleep deprivation, and examination of the relationship between multiple sleep parameters and deficit.

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Figure 1.

Flow chart of manuscript selection process

Figure 2.

The overlap of cognitive deficits in diseases with hypoxia/hypercarbia and/or sleep disturbance.

Table 1.

Conditions considered and whether hypoxia/hypercarbia and/or sleep disruption are present.

Condition	Hypoxia/Hypercarbia	Sleep disruption
OSA	Yes	Yes*
COPD	Yes	No
Insomnia (chronic)	No	Yes†
Sleep deprivation (short-term)	No	Yes†

COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnoea; *sleep fragmentation; †decreased sleep duration

Table 2.

Key neuropsychological domains, neural correlates involved in enabling cognitive function, and tasks that assess these domains.

Domain	Neural correlates	Subdomain	Example activity	Example assessment
ATTENTION <i>The capacity to direct perception, orientation and concentration on selected stimuli, and inhibit processing of unwanted stimuli</i>	Sensory input and motor output systems, the dorsolateral and midlateral prefrontal cortex, the temporoparietal junction, and the intraparietal sulcus	Simple attention	Ability to perceive and concentrate on key stimuli	Cogstate detection test
		Selective attention	Attend to key stimuli while ignoring competing stimuli	Weschler intelligence cancellation task
		Sustained attention (vigilance)	Maintain attention over a set time period	Conner’s continuous performance task
		Divided attention	Processing multiple stimuli at the same time	Test of everyday attention (Telephone directory test)
		Rapid alternating attention	Shift attention rapidly between stimuli	Test of everyday attention (Elevator counting)
MEMORY <i>The capacity to encode new information, consolidate this information and retrieve it when needed. Memory can be in verbal, visual or visuospatial modalities</i>	Hippocampus, amygdala, diencephalic structures, medial temporal lobes, entorhinal cortex and basal forebrain	Short term memory	Holding information in mind for ~30 seconds (7 +/- 2 pieces of information)	Verbal example: Digit span forwards Visual example: Spatial span forwards
		Long term memory	Encoding and consolidating memory into relatively permanent stores	Verbal example: California verbal learning test Visual example: Location learning test
		Explicit memory (declarative) – Episodic	Intentional and consciously recalled information about personal events	What-Where-When
		Explicit memory (declarative) – Semantic	Intentional and consciously recalled information about facts and knowledge	Object naming tasks
		Learning	Acquisition of knowledge and or skills	California verbal learning task learning curve across trials
EXECUTIVE FUNCTIONS <i>Processes responsible for volition, planning, purposeful action and monitoring of</i>	Frontal cortices	Updating	Updating and monitoring of working memory representations	Letter number sequencing
		Inhibition	Inhibition of dominant or pre-	NIH Examiner – inhibition

<i>performance</i>			potent responses	test
		Set shifting	Shifting between tasks or mental sets	NIH Examiner – set shifting test
		Generativity (fluency)	Efficiency of access to long term memory	Controlled oral word association task
		Fluid reasoning	Reasoning and problem solving, involving complex, higher order abstraction, problem solving and concept formation	Porteous mazes
PSYCHOMOTOR FUNCTIONS <i>Ability to co-ordinate thinking and physical movement</i>	Sensory, pre-motor and motor cortical regions, extrastriatal regions of the occipital and parietal cortices.			6-elements task
VISUOSPATIAL/ CONSTRUCTIONAL ABILITY <i>Largely automated functions which can also be directed and controlled</i>	Sensory and motor systems in the occipital and parietal lobes.			Grooved pegboard
LANGUAGE FUNCTION <i>Capacity to learn, understand and produce complex symbolic systems for communication (spoken, written and/or sign languages)</i>	Sensory and motor systems, the left posterior frontal cortex and the left posterior temporal parietal areas.			Boston naming test
GENERAL COGNITION <i>An umbrella category capturing measures of intelligence and generalised thinking skills</i>				Repeatable battery for the assessment of neuropsychological status

Table 3.

Sample size, mean age, percent gender, years of education and whether comorbidities were reported in the systematic reviews and meta-analyses used in the current paper.

		<i>N</i>	<i>Age</i>	<i>Gender</i>	<i>Education</i>	<i>Comorbidity</i>
OSA papers	<i>Fulda & Schulz (2003) (18)</i>	1,635 SRBD patients and 1,737 control subjects	SRDB = 37 and 78 y Controls = 34 and 75 y Peak for both groups = 40 and 50 years	88.3% male in patient groups and 77% male in control groups	Not reported	Not reported
	<i>Beebe et al. (2003) (8)</i>	1092 patients with OSA and 899 healthy controls	Average age OSA = 49.4 y (range 43-63 and control = 57 y (range 43-62)	OSA = 89.07% male and Controls = 83.25% male	OSA = 11.1 – 16.9 y and controls = 11.7 – 13.7 years,	BMI reported
	<i>Wallace & Bucks (2012) (9)</i>	2,294 adults with untreated OSA and 1,364 healthy controls	Average age OSA = 48.14 y (range 28-62) and average age controls = 48.65 y (range 37-63) years	Not reported	Not reported	Not reported
	<i>Olaithe & Bucks (2013) (28)</i>	1,010 participants with OSA and 551 healthy controls	OSA mean age 50.40 ± 7.43 y and controls mean age 49.46 ± 8.96 y	81% male OSA sample and 74% male controls	Sample mean education 13.73 ± 1.48 y	BMI reported
	<i>Stranks & Crowe (2016) (27)</i>	430 individuals with OSA and 381 healthy controls	OSA age 48.92 y ± 6.2 and control age 47.2 y ± 8.2	82.2% male across OSA and control groups	OSA sample 12.3 ± 1.1 y and control sample 13.1 ± 1.1	BMI reported
	<i>Aloia et al. (2004) (14)</i>	Not reported	Not reported	Not reported	Not reported	Not reported

	<i>Saunamaki & Jehkonen (2007) (11)</i>	Not reported	Mean age of patients ranged from 40 to 65 y (median: 49)	Proportion of men in the study samples ranged from 47% to 100%	Education in y ranged from 9 to 15 (median: 13 y)	Not reported
COPD papers	<i>Torres-Sanchez et al. (2015) (29)</i>	5,436 COPD patients and 564 healthy controls	Mean across the samples was 54.2 y (range 55.2-70)	44% of the sample were male	Not reported	Not reported
	<i>Dodd et al. (2010) (31)</i>	829 COPD patients and 23,842 healthy controls	Not reported	Not reported	Not reported	Not reported
	<i>Shou et al. (2012) (30)</i>	771 COPD patients and 268 healthy controls	Not reported	Not reported	Not reported	Not reported
	<i>Areza-Fegyveres et al. (2010) (32)</i>	Not reported	Not reported	Not reported	Not reported	Not reported
	<i>Hynninen et al. (2005) (33)</i>	1336 COPD patients and 114 controls	Not reported	Not reported	Not reported	Comorbid anxiety and depression reported
Insomnia papers	<i>Fortier-Brochu et al. (2012) (34)</i>	639 participants with insomnia and 558 controls	Insomnia mean age 47.3 y $\pm$ 14.9 years and controls mean age 46.1 y $\pm$ 15.3 years	Insomnia 59.2% women, controls 58.4% women	Not reported	Reported comorbid exclusion criteria used in the papers
	<i>Fulda & Schulz (2001) (7)</i>	Not reported	Not reported	Not reported	Not reported	Not reported
Sleep deprivation papers	<i>Lim & Dinges (2010) (35)</i>	1515 participants	Not reported	Not reported	Not reported	Not reported
	<i>Pilcher & Huffcutt (1996) (22)</i>	1932 participants	Not reported	Not reported	Not reported	Not reported
	<i>Philibert (2005) (36)</i>	959 physicians and 1,028 nonphysicians	Not reported	Not reported	Not reported	Not reported
	<i>Samkoff et al. (1991) (37)</i>	10,035 physicians	Not reported, though described as interns, residents and	Not reported	Not reported	Not reported

			junior doctors			
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COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnoea; BMI = body mass index; N = sample size

Table 4.

Comparison of cognitive profiles of OSA, COPD, insomnia and sleep deprivation from systematic reviews and meta-analyses

		Domain							
		Attention	Memory	Executive function	Working memory	Psychomotor function	Visuospatial/ constructional	Language function	General cognition
OSA	N of domains across studies showing a deficit /N of papers examining domain)	3/3	4/6	6/6	1/1	3/4	2/2	2/3	2/3
	Mean effect size (meta-analyses only: n = 5)	0.58	0.53	0.69	0.41	0.96	0.69	0.38	0.35
COPD	N of domains across studies showing a deficit /N of papers examining domain)	4/4	5/5	3/3	N/A	2/2	1/1	2/2	0/1
Insomnia	N of domains across studies showing a deficit /N of papers examining domain)	0/2	0/2	1/2	1/1	0/2	N/A	0/2	0/1
	Mean effect size (meta-analyses only: n = 1)	0.13	0.39	0.51	N/A	0.13	N/A	0.11	0.12
Sleep deprivation	Number of domains across studies showing a deficit /number of papers examining domain)	2/3	2/3	1/2	1/1	1/2	N/A	1/1	2/2
	Mean effect size (meta-analyses only: n = 3)	0.72	0.52	0.13	0.54	0.77	N/A	N/A	0.96

COPD = Chronic Obstructive Pulmonary Disease; OSA = Obstructive Sleep Apnoea; N/A = not explored in the present papers. Effect sizes of $d \geq 0.20$ were considered small, $d \geq 0.50$ medium, $d \geq 0.80$ large and $d \geq 1.00$ very large. Shaded cells represent domains that were considered to demonstrate cognitive deficits.

Table 5.

Summary of cognitive profiles of insomnia, COPD, OSA and sleep deprivation from systematic reviews and meta-analyses

Condition	Attention	Memory	EF	WM	PsyM	VisSpat	Lang	General
OSA	YES	YES	YES	NO	YES	YES	YES	NO
COPD	YES	YES	YES	NO	YES	NO	YES	NO
Insomnia (long-term)	NO	NO	NO	NO	NO	NO	NO	NO
Sleep deprivation (short-term)	YES	YES	NO	NO	NO	NO	NO	YES

COPD = Chronic Obstructive Pulmonary Disease; OSA = Obstructive Sleep Apnoea; EF = Executive dysfunction; WM = Working memory; PsyM = Psychomotor Speed; VisSpat = Visuospatial/Constructional ability; Lang = Language; Yes = dysfunction; No = no dysfunction or not enough evidence to suggest dysfunction; Shaded cells represent domains that were considered to demonstrate cognitive deficits.

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Table 1. Cognitive profile of untreated OSA from review and meta-analytic papers

[illegible]

	Short term (general)							C+	1/1
	Short term (verbal)		C- 0.16	C+ 0.55					1/3
	Short term (visual)		C+ 0.56 N- 0.29	C- 0.05					1/3
	Short term (visuospatial)			C+ 0.63					1/1
	Learning (verbal)			C+ 0.46					1/1
	Recognition (verbal)			C+ 1.71					1/1
	Immediate long term (verbal)	C- “Immediate” 0.09					C+		1/2

	Immediate long term (visual)	C- “Immediate” 0.09							1/1
	Delayed long term (verbal)	C+ “Retrieval” 0.17	C- 0.27	C+ 0.50			C+		3/4
	Delayed long term (visual)	C+ “Retrieval” 0.67	C+ 0.55				C+		3/3
	Delayed long term (visuospatial)			C- 0.67					0/1
	Non-verbal					C/N+ 0.79			1/1
	Verbal					C/N+ 0.39			1/1
WORKING MEMORY						C/N+ 0.41			1/1
EXECUTIVE FUNCTION			C+ 0.73			C/N+ 0.64	C+	C+	6/6

	Updating				C+ 0.91			C+	2/2
	Inhibition				C+ 1.12				1/1
	Set shifting	C+ “Mental flexibility” 0.47			C+ 0.53				2/2
	Generativity (fluency)				C + 0.59				1/1
	Fluid reasoning	C+ “Concept formation” 0.28			C+ 0.80	C/N+ “Concept formation” 0.78			3/3
<i>Psychomotor function</i>			C+ 1.21			C/N+ 0.70	C+	C-	3/4
<i>Visuospatial/constructional function</i>						C/N+ 0.69		C+	2/2
<i>Language function</i>		C+ 0.39				C/N+ 0.38		C-	2/3

<i>General cognition</i>		C+	C-						2/3
		0.24	0.13						
			N+						
			0.67						

Note: Overall effects for each included review, and for all papers reviewed marked as positive (+) if there is evidence of deficits in a cognitive domain compared to norms (N) or controls (C), and were marked as negative (-) if there was no evidence of deficits. Deficits were marked as equivocal (E) if the review, or the summarised score across reviews, was inconclusive, a blank space indicates that this domain or facet was not captured in the presented reviews. OSA = Obstructive Sleep Apnoea

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Table 2. Cognitive profiles of COPD from review and meta-analytic papers

<i>Domain</i>	<i>Subdomain</i>	<i>Systematic reviews</i>					<i>Summary</i>
		<i>Torres-Sanchez et al.</i> <i>(2015) (29)</i>	<i>Dodd et al. (2010)</i> <i>(31)</i>	<i>Shou et al. (2012)</i> <i>(30)</i>	<i>Areza-Fegyveres et</i> <i>al. (2010) (32)</i>	<i>Hynninen et al.</i> <i>(2005) (33)</i>	
<i>Attention</i>		C/N+	C/N+	C/N+	C/N+		4/4
	Simple Att.	C/N+					1/1
<i>Memory</i>				C/N+	C/N+	C/N+	3/3
	Learning	C/N+	C/N+				2/2
	Imm. LT (verbal)	C/N+					1/1
	Imm. LT (visual)	C/N+					1/1
	Imm. LT (visuospatial)	C/N+					1/1
<i>Executive function</i>		C/N+	C/N+		C/N+		3/3
	Updating	C/N+					1/1
	Generativity	C/N+					1/1
	Fluid reasoning		C/N+				1/1
<i>Psychomotor function</i>			C/N+	C/N+			2/2
<i>Visuospatial/constructional</i>			C/N+				1/1

<i>Language function</i>			C/N+		C/N+		2/2
<i>General cognition</i>						C/N-	0/1

Note: Overall effects for each included review, and for all papers reviewed marked as positive (+) if there is evidence of deficits in a cognitive domain compared to norms (N) or controls (C), and were marked as negative (-) if there was no evidence of deficits. Deficits were marked as equivocal (E) if the review, or the summarised score across reviews, was inconclusive, a blank space indicates that this domain or facet was not captured in the presented reviews. Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; Imm. = Immediate; LT = long term; Att: Attention.

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Table 3.

Cognitive profile of insomnia from review and meta-analytic papers

<i>Domain</i>	<i>Subdomain</i>	<i>Meta-analysis</i>	<i>Systematic review</i>	<i>Summary</i>
		<i>Fortier-Brochu et al. (2012) (34)</i>	<i>Fulda & Schulz (2001) (7)</i>	
<i>Attention</i>		C-		0/1
	Simple Att.	C- “Alertness” 0.04	C-	0/2
	Selective Att.	C- 0.19	E	0/2
	Sustained Att.	C- 0.16	C-	0/2
	Divided Att.	C- “Complex RT” 0.12	C-	0/2
<i>Working Memory</i>		C+ “Retention” -0.22* “Manipulation” 0.42**		1/1
<i>Memory</i>				
	Short term		C-	0/1
	Episodic	C+ 0.51**		1/1
	Learning		C-	0/1
	Procedural	C- 0.26		0/1
<i>Executive function</i>			C+	1/1
	Set shifting	C- “Flexibility” 0.16		0/1
	Generativity	C- 0.19	C+	1/2
	Fluid reasoning	C+ “Problem solving” 0.42**		1/1

<i>Psychomotor function</i>		C- 0.13	C-	0/2
<i>Visuospatial/constructional</i>				0/0
<i>Language function</i>		C- 0.11	C-	0/2
<i>General cognition</i>		C- 0.12		0/1

Note: Overall effects for each included review, and for all papers reviewed marked as positive (+) if there is evidence of deficits in a cognitive domain compared to norms (N) or controls (C), and were marked as negative (-) if there was no evidence of deficits. Deficits were marked as equivocal (E) if the review, or the summarised score across reviews, was inconclusive, a blank space indicates that this domain or facet was not captured in the presented reviews. Abbreviations: Att: Attention.

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Table 4. Cognitive profile of sleep deprivation from review and meta-analytic papers

<i>Domain</i>	<i>Subdomain</i>	<i>Meta-analyses</i>			<i>Sytematic reviews</i>	<i>Summary</i>
		<i>Lim & Dinges (2010) (35)</i>	<i>Pilcher & Huffcutt (1996)</i> (22)	<i>Philibert (2005) (36)</i>	<i>Samkoff et al. (1991) (37)</i>	
<i>Attention</i>					C/N-	0/1
	Simple Att.	C/N+ “Lapses” 0.762** “RT” 0.732**				1/1
	Sustained Att.			C/N+ “Vigilance” 1.330**		1/1
	Divided Att.	C/N+ “Complex attention” “Accuracy” 0.479** “RT” 0.312**				1/1
<i>Working memory</i>		C/N+ “Accuracy” 0.555** “RT” 0.515**				1/1
<i>Memory</i>				C/N+ 0.806**	E	1/1
	Short term	C/N+ “Recall” 0.383* “Recognition” 0.378*				1/1
<i>Executive function</i>					C/N-	0/1
	Fluid reasoning	C/N+ “Reasoning” 0.125				1/1
<i>Psychomotor function</i>			C/N+ 0.77**		C/N-	1/2

<i>Visuospatial/constructional</i>						0/0
<i>Language function</i>					C/N-	1/1
<i>General cognition</i>			C/N+ 1.36**	C/N+ 0.564		2/2

Note: Overall effects for each included review, and for all papers reviewed marked as positive (+) if there is evidence of deficits in a cognitive domain compared to norms (N) or controls (C), and were marked as negative (-) if there was no evidence of deficits. Deficits were marked as equivocal (E) if the review, or the summarised score across reviews, was inconclusive, a blank space indicates that this domain or facet was not captured in the presented reviews. Abbreviations: LT = Long term; Att. = Attention; Imm = Immediate.

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Table 5

Descriptive details of the papers included in the meta-review

	<i>Type of paper</i>	<i>Pre-treatment papers (Participants)</i>	<i>Cognitive domains and tasks (if reported)</i>
<i>Obstructive Sleep Apnoea</i>			
Aloia, M.S., Arnedt, J.T., Davis, J.D., Riggs, R.L., Byrd, D. (2004). Neuropsychological sequelae of obstructive sleep apnoea-hypopnoea syndrome: A critical review. <i>Journal of the International Neuropsychological Society</i> ; 10: 772-85. (10)	Systematic review Pre-treatment group comparisons, treatment efficacy (CPAP) studies and correlational studies	N = 12 empirical articles	Global cognition (full scale, verbal and /or performance IQ, MMSE, estimates of premorbid intelligence); Attention (digit span, CPT, PASAT, letter cancellation task); Executive functions (WCST, Halstead categories test, TMTB, COWAT, Stroop Test, and Mazes); Language (Boston naming test, Category fluency); Memory (CVLT, ROCF, Logical Memory and Visual Reproduction Subtests [WAIS]); Construction (intersecting pentagons

			[MMSE], Block Design [WAIS], and the ROCF); Psychomotor function (Grooved pegboard, finger tapping test)
Beebe, D.W., Groesz, L., Wells, C., Nichols, A., McGee, K. (2003). The Neuropsychological Effects of Obstructive Sleep Apnoea: A Meta-Analysis of Norm-Referenced and Case-Controlled Data. <i>Sleep</i> ; 26(3): 298-307. (8)	Meta-analysis Pre-treatment group comparisons with a) controls, and b) norms	N = 25 empirical studies and unpublished papers (1092 Pts)	Intelligence (full scale WAIS/WAIS-R, Shipley Institute of living scales); Verbal ability (Verbal IQ or subtests of WAIS/WAIS-R); Visual ability (Performance IQ of WAIS/WAIS-R, Hooper VOT, ROCF Copy, Raven matrices); Short-term verbal memory (Buschke SRT, WMS logical memory or word pairs, RAVLT, CVLT free); Short-term visual memory (CVMT, ROCF Immediate Recall, Benton VRT or free recall, WMS or WMS-R Figural Memory); Long-term verbal memory (Delayed recall trials of the short-term verbal memory measures); Long-term visual memory (Delayed recall trials of the short-term visual memory measures);

			Executive functioning (Digit Span, Visual Memory Span, Seashore Rhythm, COWAT, PASAT, Digit Symbol, TMT B, Stroop, WCST, Category Test); Motor functioning (finger tapping, Purdue pegboard, grooved pegboard); Vigilance (Steer clear, PVT, CPT)
Fulda, S., Schulz, H. (2003). Cognitive dysfunction in sleep related breathing disorders: A meta-analysis. <i>Sleep Research</i> ; 5(1): 13-43. (18)	Meta-analysis Pre-treatment group comparisons with norms and/controls	N = 28 empirical studies and unpublished papers (1635 Pts)	Perception (Hooper visual organisation test, Thurstone visual matching test, graphesthesia, Benton facial recognition task, Sensory motor task); Simple reaction time/Alertness (visual RT, Choice RT, CFF, phasic alertness, tonic alertness); Attentional span/Short term attention (Digit span forward, Hiskey-Nebraska blocks, Corsi block tapping task, Double encoding task); Focused attention (TMT, Symbol digit substitution and digit symbol substitution, letter and digit cancellation)

			tasks); divided attention (serial addition, digit subtraction, N-back tasks, PASAT, Wiener divided attention, visual and/or auditory tracking tasks); Selective attention (Visual complex reaction time, Dichotic listening task, Wiener selective attention and Q11, Stroop); Sustained attention (FCRRT, PVT, CPT, sustained attention task, continuous attention, modified sustained attention task); Vigilance (Muggeburg test, Quatember Maly, Parasuraman vigilance task, Vigilance test, CFF); Psychomotor speed (Finger tapping, digit copying task, sensory motor task); Manual dexterity and speed (Grooved pegboard, purdue pegboard); Constructional performance (ROFC, Bender Gestalt test, extended range drawing test, Block design, object assembly); Immediate recall-visual (WMS
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			<p>figural memory, Benton VRT, ROFC)</p> <p>Immediate recall-verbal (CVLT, WMS logical memory, AVLT); Learning verbal and visual (CVLT list learning, WMS associate learning, AVLT learning, Verbal learning test, visual learning test); Free recall long delay visual (WMS figural memory, ROFC); free recall long delay verbal (CVLT, WMS logical memory); forgetting visual (Visual learning test, WMS figural memory); forgetting verbal (verbal learning test, WMS logical memory, AVLT % retained); Recognition (AVLT recognition); Concept formation in visual (Raven progressive matrices, Category test); Concept formation in verbal (Simulation); Sort and shift (WCST); Reasoning (Comprehension, 20-question procedure, Telegram 2, Arithmetic, Picture</p>
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			arrangement); Executive functions (Mazes, Towers); Verbal fluency (COWAT, Verbal fluency); Verbal expression (WAIS-R vocabulary, Boston naming task); Composite measures (WAIS, WAIS-R full/verbal/performance, MMSE, Processing speed index, factor psychomotor efficiency)
Olaithe, M., Bucks, R.S.B. (2013). Executive dysfunction in OSA before and after treatment: A meta-analysis. <i>Sleep</i> ; 36(9): 1297-1305. (28)	Meta-analysis Pre-treatment group comparisons, treatment efficacy (CPAP) studies and correlational studies	N = 35 (1010 Pts)	Shifting (WCST, TMT B, switching task); Updating (N-back tasks, Digit span BW, WAIS-R Arithmetic, ANAM Mathematical processing or running memory); Inhibition (Towers, Stroop task, Go No-go task); Generativity (Verbal fluency tasks); Fluid reasoning (Mazes, Ravens progressive matrices, picture completion, WAIS-R picture arrangement or block design or similarities, stockings of Cambridge, object assembly, clocks, twenty questions, ANAM matching to sample or logical relations, five

			point task design)
Saunamaki, T., Jehkonen, M. (2007). A review of executive functions in obstructive sleep apnoea syndrome. <i>Acta Neurol Scand</i> ; 115: 1-11. (11)	Systematic review	N = 29 Pre-treatment group comparisons, treatment efficacy (CPAP) studies	Executive function (phonological or semantic fluency, TMT A and B, Digits FW and BW, WCST, Stroop, Towers, ROCF, Corsi's block tapping task, Raven's progressive matrices, Mazes, double encoding task, twenty questions procedure)
Wallace, A., Bucks, R.S. (2012). Memory and Obstructive Sleep Apnoea: A Meta-analysis. <i>Sleep</i> : 36 (2): 203-20. (9)	Meta-analysis Pre-treatment group comparisons with norms and/controls	N = 42 (2294 Pts)	Verbal immediate recall (Buschke SRT, CVLT, RAVLT, WMS logical memory, verbal recall, serial verbal learning task); Visual immediate recall (WMS figural memory); visuospatial immediate recall (Benton VRT, ROCF, WMS figural memory or visual reproduction); Verbal delayed recall (AVLT, Buschke SRT, CVLT, Hopkins VLT, Serial verbal learning test, test of prose memory, WMS logical memory); Visuospatial delayed recall (ROCF, WMS figural memory or visual

			reproduction); Verbal learning (Buschke SRT, CVLT< HVL, HVL-R, RAVLT, Serial verbal learning task); Visuospatial learning (Brief visuospatial memory test revised); Verbal recognition (CVLT, RAVLT, WMS logical memory recognition, recollection of temporal memory)
Stranks, E.K., Crowe, S.F. (2016). The Cognitive Effects of Obstructive Sleep Apnea: An Updated Meta-analysis. <i>Arch Clin Neurol. Epub ahead of print. (27)</i>	Meta-analysis	N = 19	Attention (WAIS Digit Span FW, Letter Cancellation, Corsi, PASAT, TMT A, N-Back, Double Encoding Task, CANTAB Spatial Span test, Repeated Psychometric Measures (visualization subtest)); Concept formation (WAIS-R Picture Arrangement, similarities, picture completion, Raven's Advanced Progressive Matrices); Construction (ROFC (copy), WAIS-R Block Design, Object Assembly, Bender Visual Motor Test, Corsi supraspan learning ability); Executive function (Mazes, Stroop,

			<p>WCST, Tower of Toronto, Intra-Extra Dimensional set-shifting, Stockings of Cambridge, Porteus Maze, Five-point test);</p> <p>Motor control/performance (Purdue Pegboard, Mirror Tracing Task); Non-verbal memory (ROFC (recall), WMS Figural Memory, CANTAB Self-Ordered Spatial Memory Task); Perception (Digit Cancellation task); Psychomotor speed (DSST, Symbol Digit Modalities Test);</p> <p>Speed of processing (TMT B, Critical Flicker Fusion test, Zimmermann-Fimm Test battery for Attentional Performance (Flexibility Test subtest)); Verbal function/language (WAIS-R Vocabulary, Information, Boston Naming Test); Verbal memory (WMS Logical Memory, Rey List, RAVLT, serial verbal learning test, verbal learning test (using selective reminding</p>
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			procedure of Buschke), CVLT); Verbal reasoning (COWAT, verbal fluency task); Working memory (WAIS Digit Span backwards, WAIS Arithmetic CANTAB spatial Working memory)
<i>Sleep deprivation</i>			
Lim, J., Dinges, D.F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. <i>Psychological Bulletin</i> ; 136(3): 375-89. (35)	Meta-analysis	N = 70	Simple attention (e.g., Psychomotor vigilance test); Complex attention (e.g., Stroop test, Continuous performance test); Processing speed (e.g., Digit symbol substitution, WAIS); Working memory (e.g., Sternberg working memory task); Short term memory (e.g., Logical memory, WMS); Reasoning and crystallised intelligence (e.g., Raven's Advanced Matrices, Baddeley's grammatical reasoning test); Verbal fluency (e.g., Verbal fluency)
Pilcher J.J., Huffcutt A.I. (1996). Effects of sleep deprivation on performance: A meta-analysis. <i>Sleep</i> : 19(4); 318-326. (22)	Meta-analysis	N = 19 (1932)	Psychomotor; General cognition

Samcoff and Jacques, 1991, A review of studies concerning effects of sleep deprivation and fatigue on residents' performance. <i>Acad Med</i> ; 66(11): 687-93. (37)	Systematic review	N = 23	Psychomotor (Manual dexterity task, Purdue pegboard); Attention (choice reaction time, digit symbol, Neisser letter search, PASAT, TMT, Critical flicker fusion, Vigilance reaction time); Memory (Immediate recall, Sternberg short memory, Delayed story recall); Executive functions (Minnesota form board, WCST, Raven's progressive matrices, Stroop); Language (Bradley grammatical reasoning); Visuospatial (Haptic scoring task)
Philibert, I. (2005). Sleep loss and performance in residents and non-physicians: A meta-analytic examination. <i>Sleep</i> : 28(11); 1392-1402. (36)	Meta-analysis	N = 60	Cognition; Memory; Vigilance
<i>Chronic Obstructive Pulmonary Disease (COPD)</i>			
Torres-Sánchez, I., Rodríguez-Alzueta, E., Cabrera-Martos, I., López-Torres, I., Paz Moreno-Ramírez, M., Valenza, M.C. (2015) Cognitive impairment in COPD: a systematic review. <i>J Bras Pneumol</i> ; 41(2): 182–190. (29)	Systematic review	N = 16	Perception (block design, bell's test, raven's progressive matrices, Corsi block tapping test, Albert's test, copying geometric drawings with/out landmarks, computer

			<p>aided risk simulator); Attention (digit span, digit symbol, semantic verbal fluency, letter verbal fluency, attention network test, verbal word span, Computer aided risk simulator);</p> <p>Memory and learning (Rey complex figure test copy and recall, WMS, Rey auditory verbal learning test, word lists learning WMS, delayed recall WMS, delayed recognition WMS, logical memory WMS, verbal and non-verbal learning Vienna test system, Corsi block tapping test, verbal word span test, Rey auditory 15 word learning test, immediate visual memory test); Language (verbal fluency, sentence construction, phonemic verbal fluency test);</p> <p>Abstract thinking and executive functions (TMT, letter-number sequencing, digit symbol, symbol search, digit span, symbol coding, semantic verbal fluency, letter</p>
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			verbal fluency, stroop, attention network test,); Intelligence (Weschler test of adult reading, WRAT); General global screening (MMSE, Montreal cognitive screening, dementia rating scale, mental deterioration battery, 10-item Hokinson abbreviated mental test)
Dodd, J.W., Getov, S.V., Jones, P.W. (2010). Cognitive function in COPD. <i>Eur Respir J</i> ; 35(4): 913-22. (31)	Systematic review	N = 17	Attention; Perception; Memory and learning; verbal and language; construction; concept formation and reasoning; Executive functions; Motor function
Shou, L., Ostergaard, B., Rasmussen, L.S., Rydahl-Hansen, S., Phanareth, K. (2012). Cognitive dysfunction in patients with chronic obstructive pulmonary disease – A systematic review. <i>Respir Med</i> ; 106(8): 1071-81. (30)	Systematic review	N = 15	Memory and learning (memory efficiency test, WMS, VMLT, Rey's auditory verbal memory test, story recall, selective reminding, mental deterioration battery); Attention (digit span subtest, WRG S5, Cognitrone S2, WDG, Stroop); Intelligence (ZVT, MWT, WAIS, WRAT, Groningen

			intelligence test); Information processing speed and coordination (TMTB, Halstad-Reitan test battery for adults, TAP, grooved pegboard, speech sounds perception test, Lafayette repeatable battery, Finger tapping test); Verbal fluency (COWAT, Animal naming, sentence construction, aphasia screening test, boston naming test, mental deterioration battery); Visual attention (Raven's progressive matrices, Benton visual retention test, colour trail test, albert's test, copying drawings, mental deterioration battery); Auditory attention (seashore rhythm test); Conceptual function (WCST)
Areza-Fegyveres, R. Kairalla, R.A., Carvalho, C.R.R., Nitrini, R. (2010). Cognition and chronic hypoxia in pulmonary diseases. <i>Dement Neuropsychol</i> ; 4(1): 14-22. (32)	Systematic review		Memory; Language; Attention; Executive function; abstract thinking
Hynninen, K.M.J., Breivtve, M.H., Wiborg, A.B., Pallesen, S., Nordhus, I.H. (2005). Psychological characteristics of patients with	Systematic review	N = 81	General cognition (MMSE); Memory

chronic obstructive pulmonary disease: A review. <i>Journal of psychosomatic research</i> ; 59: 429-43. (33)			
<i>Insomnia</i>			
Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers. H., Morin, C.M. (2012). Insomnia and daytime cognitive performance: A meta-analysis. <i>Sleep Medicine Reviews</i> ; 16; 83-94. (34)	Meta-analysis	N = 24 (639 pts)	<p>General cognition (MMSE, Groningen intelligence test, Dutch Adult reading test, WAIS vocabulary, NART, WAIS FSIQ);</p> <p>Psychomotor functions (Finger tapping, hand tremor, line tracing, card sorting, purdue pegboard); Perceptual functions (visual vigilance, critical flicker fusion, emotional stroop, line judgement, card sorting); Simple Attention (Simple vigilance task, Simple alertness task, simple reaction time, brake reaction time, sustained attention); Complex attention (complex reaction time, CPT, choice RT, stop signal procedure, 4 choice RT); Attention information processing (DSST); Attention selective (complex vigilance task, CPT, Go</p>

			<p>No-go task, integration of t2 dimensions, TMT-A); Attention divided (Continuous performance task, divided attention);</p> <p>Attention sustained (complex vigilance task, vigilance task, visual or auditory vigilance task, vigilance detection task, Wilkinson 4 choice RT); Working memory (memory and search tasks, Sternberg short term memory scanning, recognition of words, memory span, digit span FW, memory and search task, rapid visual information processing, 2-back working memory task); Episodic memory (declarative memory task, Williams word memory task, Hopkins VLT, 16 time memory task, verbal paired associates, selective reminding task, verbal paired associates); Procedural memory (mirror tracing task); Executive functions verbal</p>
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			fluency (verbal fluency); Executive functions flexibility (switching attention task, emotional stroop, stroop colour-word, stop signal procedure, TMT-B); Executive functions problem solving (WCST, Mazes); Verbal functions (Proofreading task, naming)
Fulda and Shulz, (2001), Cognitive dysfunction in sleep disorders. <i>Sleep medicine reviews; 5(6): 423-45. (7)</i>	Systematic review	N = 18	Perception (Graphesthesia, Hooper Visual Organization Test, Thurstone Visual Matching Test, Sensory motor task, Line judgement, Physical match); Alertness (CFF, Simple reaction time, Simple auditory reaction time, Choice reaction time, P300 paradigm); Attention span (Digit span FW/BW, Corsi Block Tapping Task, Spatial span FW/BW, Knox Cube Imitation Test, Double-encoding task, visual span, verbal span, double span); Focused attention (TMT A/B, SDST, DSST, Letter

			<p>cancellation, d2 cancellation task, Digit cancellation, MAST, Strub And Black's List Of Letters, Visual search, Serial search task, Selective attention, Q11-WTB, Selective attention task); Divided attention/mental tracking (Divided attention-WTB, Divided attention-TAP, Divided attention task, PASAT, Stroop Color Word Test, Digit subtraction, Mental tracking, subtraction, Serial addition, Wilkinson Addition Task, Memory addition task, Letter number sequencing, Mental tracking alphabet, Continuous tracking task, Word list monitoring); Other complex attention tasks (General response latency-combined measure, Switching Attention Test, Complex reaction time, Go-No Go test, Shifting of attention, Krakau Visual Acuity, Two choice reaction time, reaction time after</p>
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			<p>warning tone, anticipatory responses, CNV Paradigm); Sustained attention (Modified sustained attention test, CPT, FCRTT, Continuous Attention Test, PVT, Continuous Attention Test, Wilkinson Addition Task-20 min, DSST-20 min); Vigilance (Mackworth clock, Muggeburg Test, Vigilance test, Auditory vigilance, Auditory vigilance test, Wilkinson auditory vigilance test, CFF-10 hours); Motor functions (Finger tapping task, Grooved Pegboard Task, Purdue Pegboard Task, Pegboard, Grunberger Fine-Motor Activity Test, Sensory motor task, reaction time, Hand tremor, Line tracing Constructional performance); Copying (ROCF, Bender Gestalt Test); Building and assembling (WAIS-R Block Design, WAIS-R Object Assembly); Memory; Visual immediate</p>
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			<p>recall (WMS Figural Memory, Rey-Osterrieth figure); Verbal immediate recall (WMS Logical Memory, CVL), WMS Verbal Paired Associates, Williams Word Memory Test, Selective Reminding Test, Word List Recall); Learning (CVLT List learning, WMS Associate learning, AVL, Verbal learning test, selective reminding procedure, WMS Verbal paired associates, learning rate, Selective reminding test, Verbal learning, Visual learning test);</p> <p>Visual delayed free recall (Rey-Osterrieth figure, WMS Figural memory; Verbal delayed free recall (CVLT, WMS Logical memory, AVL, WMS Verbal Paired Associates, Verbal delayed recall;</p> <p>Forgetting (Visual Learning Test, % forgetting, Verbal Learning Test, % forgetting, WMS Figural Memory, %</p>
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			retained, WMS Logical Memory, % retained, AVLT % retained; Other memory tasks (WMS Logical Memory, WMS Figural Memory, CVLT, Factor memory, AVLT recognition, Verbal Learning And Memory Test, Pursuit Rotor Learning-trials, Spatial Working Memory Task, Word list recognition, Word recognition, Figure recognition, Numerical memory test, Delayed word list relearning, Difference between recall and recognition, Short-term memory, Long-term Memory, Word list frequency estimation, incidental memory, Sternberg Memory Scanning Task, WMS Paired Associates Cued Recall); Concept formation (WAIS-R Similarities, WCST, Card sorting); Reasoning (WAIS-R Picture arrangement, WAIS-R Comprehension, 20 question task, Optimal telegram task,
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			<p>Logical reasoning, Baddeley's Logical Reasoning Task; Executive functions (Mazes, Tower puzzles, Tower of Toronto, Porteus Mazes); Verbal functions and language skills; Verbal fluency COWAT, Verbal fluency; Other executive function tasks (WAIS-R Vocabulary, WAIS-R Information, Boston Naming Test, Proofreading, Word detection, Revised Token Test, Stroop Test, Semantic match, Naming test); Composite measures (WAIS-R Full scale, WAIS-R Verbal scale, WAIS-R Performance scale, WAIS-R Vocabulary and Block Design, MMSE, Factor psychomotor efficiency)</p>
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Note: IQ = Intelligence quotient; MMSE = Mini Mental State Exam; CPT = continuous performance test; PASAT = paced auditory serial addition task; WCST = Wisconsin card sorting test; TMT = Trail Making Test; COWAT = Controlled Oral Word Fluency; CVLT = California verbal learning test; ROFC = Rey-Osterrieth Complex Figure; WAIS = Weschler Adult Intelligence Test; WAIS-R = Weschler Adult Intelligence Test Revised; VOT = Visual Organisation Test; SRT = Selective Reminding Test; WMS = Weschler Memory Scale; WMS-R = Weschler Memory Scale Revised; RAVLT = Rey Auditory Verbal Learning Test; CVMT = Continuous Visual Memory Test; VRT = Visual Retention Test; PVT = Performance Validity Test; RT = Reaction Time; CFF = Critical Flicker Fusion; AVL T = Auditory Verbal Learning Test; ANAM = Automated Neuropsychological Assessment Metrics; FW = forwards; BW = backwards; CANTAB = CAMbridge Neuropsychological Test Automated Battery; WRAT = Wide Range Achievement Test; WRG-S5 = Wiener Reaktionsgerät; WDG = Wiener Determinationsgerät; ZVT = number connection test; MWT = Mehrfachwahl-Wortschatz-Test; TAP

= Test Battery for Measuring Attention; DSST = Digit Symbol Substitution Task; SDST = Symbol Digit Substitution Test; MAST = Memory And Search Task; WTB = Wiener Test Battery; CNV = *contingent negative variation*; FCRTT = Four-Choice Reaction Time Test; PVT = Psychomotor Vigilance Device.