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Review Article

Obstructive sleep apnea, depression and cognitive impairment

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a severe disorder with a high prevalence. Psychiatric comorbidities, especially depressive symptoms and cognitive dysfunction, are often described in OSA patients. This narrative review aims to examine: (1) the relationship between obstructive sleep apnea syndrome (OSAS) and depressive and cognitive symptoms, and (2) the effect of OSAS treatment on psychiatric symptoms.

Method: Articles that were published between January 1990 and August 2018 were searched and extracted via PubMed, and Web of Science databases. Authors analyzed the papers and its references using the following keywords: obstructive sleep apnea, depression, cognitive dysfunction, anxiety disorders, and continuous positive airway pressure (CPAP). A total of 632 articles were nominated. After the selection according to the inclusion and exclusion criteria, 172 articles were chosen. After complete inspection of the full texts, finally, 58 papers were selected. Secondary papers from the reference lists of the primarily designated papers were also searched, assessed for suitability, and added to the first list of the papers ($n = 67$). In total, 125 papers were included in this review.

Results: There is a significant overlap in depressive, anxious and OSA symptoms. Studies also show that attention, working memory, episodic memory, and executive functions are decreased in OSA. Conversely, most of verbal functions remain intact and variable results are found in psychomotor speed. Several studies implicated that in some fields of cognitive functions (eg, attention) deficit caused by untreated OSA can be irreversible and shows only partial recovery after a period of treatment with CPAP.

Conclusions: Untreated OSA impacts affective disorders, and often leads to decline of cognitive functions or even leads to permanent brain damage. Further studies are needed to analyze the connection between OSA and affective disorders, anxiety disorders and its effect on cognitive functions more thoroughly, especially in the context of CPAP treatment.

1. Introduction

Obstructive sleep apnea (OSA) has been classified as a sleep breathing disorder which contributes to oxidative stress. OSA occurs in at least 10% of the population, and leads to higher morbidity and mortality; nevertheless, associations between OSA severity and psychological or psychiatric problems remain unclear. OSA is characterized by repeated cessation or significant restrictions of airflow (apnea and hypopnea) present in sleep accompanied by oxygen desaturation and arousals [1]. Currently, it is the most common sleep disorder of breathing [1,2]. Craniofacial disharmony is a central risk aspect for the OSA [3]. The fatty accumulation in the pharynx may have a role in some very obese individuals [3]. The most OSA is linked to a narrow high-arched hard palate and midface hypoplasia with retro-positioning of the maxilla and chin (bringing the soft palate and tongue closer to the back of the throat [4]). The structural disproportions among the skeletal craniofacial and soft tissue structures disturb pharyngeal airway morphology in

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OSA patients. The proportions of the nasopharynx, pharyngeal length, and the cross-sectional area at the hard palate level, were linked with the severity of OSA [5].

Although (hetero) anamnestic information may be collected to determine the diagnosis of OSA, apnea hypopnea index (AHI) polysomnography (PSG) is a gold standard for proper diagnosis. AHI refers to the number of apnea or hypopnea episodes recorded per hour of sleep. An AHI of 5–14 indicates mild, 15–30 moderate and ≥30 severe OSA. Hypopnea and apnea interrupt deep sleep and rapid eye movements (REM) phase and cause sleep pattern fragmentation [6]. After awakening, patients do not feel relaxed and remain tired during the day. Night time symptoms include snoring, breathing breaks, feeling sick, excessive salivation, excessive sweating, gastroesophageal reflux, urination during the night, dry mouth and headache [7,8]. Day time symptoms include excessive sleepiness, loss of energy, irritability [9], withdrawal from social activities, difficulty in concentrating [10], cognitive dysfunction [11,12], anxiety or depressive mood problems [13], and psychomotor changes [9,14]. These symptoms show a marked similarity to the symptoms of major depressive disorder [15,16]. Up to 63% of patients with OSA have depressive symptoms [13,16,17]. Therefore, many sleep laboratories regularly evaluate the depressive symptoms of their patients using screening questionnaires [8]. The similarity in the phenotypic expression of OSA and depressive disorders may lead to misdiagnosing sleep apnea for depressive disorder and misuse of antidepressant therapy [18,19]. Diagnostics is performed in sleep laboratories. The most effective treatment is considered to be positive airway pressure (PAP) treatment – the most common mode of therapy is continuous positive airway pressure (CPAP) derived via different types of masks [20–22]. Surgical treatment might be efficient in some cases, especially in mild to moderate OSA in non-obese patients [5].

The prevalence of OSA in adults (39–59 years) is estimated to be between 2% and 14%, but in individuals with age over 60 years it is as high as 20% [2,23,24]. A critical epidemiological analysis of limited home polysomnography in the United States showed that the prevalence of OSA, defined by AHI > 15, was approximately 18% in the general population [25]. OSA significantly reduces the quality of life (QoL) [22,24]. It is also a risk factor for other health problems such as increased prevalence of cardiovascular diseases, hypertension, sudden death, and psychiatric conditions like depression, irritability, memory and cognitive impairment [24–28]. Many studies have confirmed that obesity, age, sex, snoring, pharyngeal anatomy abnormalities, and cephalometric characteristics may be risk factors for OSA [5,29,30].

In the literature, OSA is discussed as possible comorbidity of affective and cognitive disorders [31–33]. When unrecognized, OSA may worsen the symptoms of psychiatric disorders and prevent achieving of remission [32]. OSA is often considered and diagnosed late, even when snoring and apneas are noticed by medical staff. Studies combining untreated OSA with range of psychiatric disorders have emerged [34,35]. Recently, several studies connected untreated obstructive sleep apnea with a range of psychiatric disorders [36–39]. This confirms that comorbid OSA may worsen symptoms of affective disorders. OSA shares many symptoms with depression (concentration disturbances, energy loss, and increased fatigue) and leads to the deepening of depressive symptomatology and the development of cognitive deficits [32,38–41]. Untreated comorbid OSA leads to poor adherence to drug therapy, and in contrary, treatment of OSA improves the symptoms of depression [40,42–44].

Due to the contraindication of hypnotics and benzodiazepines in OSA, initial depressive treatment periods with polypharmacy may lead to a rapid worsening of OSA symptoms [45]. However, this contraindication can be minimized by using CPAP therapy during the period of sleep in severe depressive disorders.

The aim of the narrative review is to examine: (1) the relationship between OSAS and depressive and cognitive symptoms, and (2) the effect of OSAS treatment on psychiatric symptoms.

2. Method

Articles were acquired via PubMed and Web of Science published in the years between January 1990 and August 2018 were extracted. This article is narrative review, which describes and discusses the state of the knowledge of a topic of the OSA relation to psychiatric and cognitive problems from the contextual point of view. It consists of the critical examination of the literature published in PubMed, and Web of Science. Authors made a series of literature searches using the following keywords or items in indexed fields: obstructive sleep apnea, depression, cognitive dysfunction, anxiety disorders, and CPAP. The selected papers met the following inclusion criteria: (1) published in peer-reviewed journals; (2) studies in humans; or (3) reviews on the related topic; and (4) English language. The exclusion criteria were: (1) abstracts from conferences; (2) commentaries; and (3) subjects younger than 18 years. In addition, further articles were chosen from the reference lists of primary articles. As shown in Fig. 1 we searched for literature in other systematic reviews and meta-analyses. The total of 632 articles were nominated by primary assortment using keywords in different combinations. After the selection according to the inclusion and exclusion criteria, 172 pieces were chosen. After a complete inspection of the full texts, 58 papers were selected. Secondary documents from the reference lists of the primarily designated papers were searched, assessed for suitability, and added to the first list of the papers ($n = 67$). In total, 125 papers were included in the review process (Fig. 1), in consistence with the PRISMA Guidelines [46].

Because of narrative character of the review, we did not use the assessing risk of bias of the individual studies, nevertheless, all studies were scrutinized by two reviewers, who discuss the methodology of the studies and select only studies with good enough methodology.

3. Results

3.1. Depression in patients with OSA

Psychiatric comorbidities, especially depressive symptoms or depressive disorders, are often described in OSA patients [26,47]. Concerning emotional well-being, the disturbed sleep pattern negatively affects the stress system and thus increases the susceptibility of OSA individuals to depression [47–49]. The study of Kang et al. [50], revealed damages at insular cortex with correlation to symptoms of depression and anxiety (Hamilton depression scale and Hamilton anxiety scale) in OSA individuals which were proven using magnetic resonance imaging (MRI).

Depressive disorders and sleep related breathing disorders very often occur together [38,51]. Sleep apnea occurs more frequently in patients with a primary diagnosis of depressive disorder compared to the overall population [8,49,52–55]. Evidence of the link between depression and OSA varies. Some authors report that patients with OSA do not show a clinically significant degree of depression or have a severity of depressive symptoms higher than healthy controls [56–58], or patients with other chronic diseases [59]. In an investigation of 60 patients with OSA, Lee [56], found that none of them had reached the diagnostic criteria for depression. In further research in 112 patients with OSA, the severity of depression was correlated with age, body mass index, and sleep parameters [60]. However, the severity of OSA was not associated with the severity of depression scores. Similar results were found in

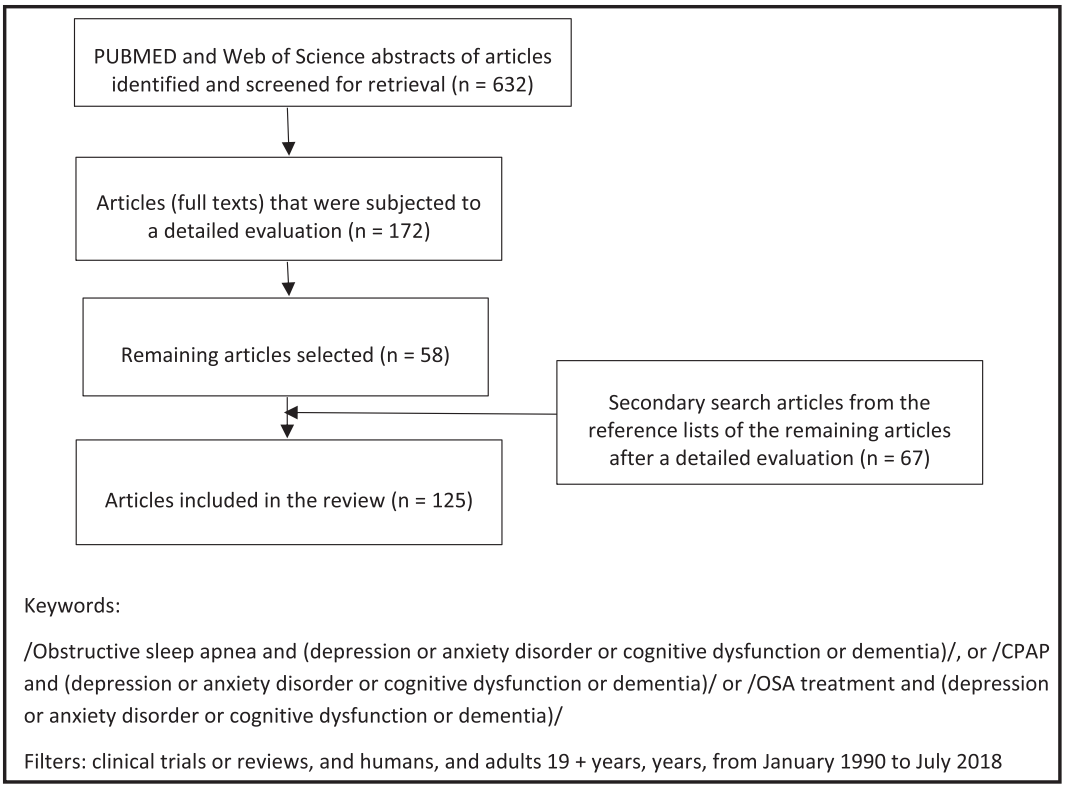

Fig. 1. Summary of the selection process.

a study in 2271 patients investigated for sleeping disorders related to breathing [61]. In this group, the presence of OSA was not associated with depression or anxiety [61].

On the other hand, other studies have found that OSA may be associated with clinically significant depression [26,62] or increased severity of depressive symptoms [20,47,52,58,63–65]. That may be a direct consequence of sleep fragmentation or secondary to the social impact of this disease. In one study, depressive symptoms levels were more severe when OSA and night hypoxaturation were more pronounced [66]. Notably, Ong et al. [52], showed that 39% of 51 patients with insomnia and depression also met the OSA criteria. Most of the studies quantify depressive symptoms by questionnaires, most frequently Beck depression inventory, or objective scales like Hamilton depression and Hamilton anxiety scales. The major disadvantage of questionnaires and objective scales are that they measure the intensity of symptoms but not presence of depressive disorders [65].

Daytime functioning may be impaired due to energy loss, fatigue, depressed mood, sleepiness, irritability, and concentration difficulties, which are the main symptoms of affective disorders. Therefore, OSA diagnosis can easily be overlooked in patients with depression [7]. Moreover, sleepiness itself is one of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria of depressive disorder and also overlaps with the criterion of fatigue or loss of energy [7]. These diagnostic complexities may delay proper diagnosis of OSA in patients with depression. Also, the questionnaire recognizes some depressive symptoms even in individuals of general “healthy” population [66]. Several symptoms often reported by the patients with OSA, such as anergia, anhedonia, poor concentration, decreased libido, and cognitive deficiency may share underlying mechanisms with depression. As reported in one study, the severity of OSA was significantly correlated to the score of Beck depression inventory, subjective sleepiness on the ESS and the BMI [15]. This might suggest that the shared link between OSA and depression could be impaired sleep, leading to overlapping in symptoms. Another possible link between OSA and depression could be obesity. According to several studies, there is an increased prevalence of depression among obese patients [67–69], and obesity is the major independent risk factor for OSA. The third possible link could be the role of chronic inflammation both in OSA and depressive patients. There is evidence of chronic inflammation in OSA and its decrease after CPAP treatment [72,73], and studies are corroborating the role of chronic inflammation in depressive patients [76].

The most crucial question is whether the occurrence of depressive symptoms is directly associated with OSA alone or it is the result of further disturbances such as drowsiness and worsening of the condition associated with apnea and fragmentation of sleep [37,68–74]. It is assumed that OSA induces depression in some individuals, but it is not known whether this depression is a primary clinical phenomenon, or a secondary consequence of the overlapping physical symptoms shared by both disorders [75]. Moreover, reduced quality of life in patients with OSA may impair their overall perception of health and emotional well-being and contribute to the development of depression [74,77]. Some of the symptoms often reported by patients with OSA, such as lack of energy, loss of interest, poor concentration, decreased libido, and cognitive insufficiency, may coincide with the same symptoms described in depressed patients and may be associated with daytime somnolence [15,39]. For this reason, the assessment of the link between depression and OSA can be difficult because it is difficult to distinguish the symptoms of OSA itself and the symptoms of depression, which may be very similar in some cases. One possible explanation for the high scores of depressive symptoms in questionnaires in patients with OSA is that these measurements include items focused on the shared depression and OSA symptoms.

Instead, they can testify to the severity of OSA rather than depression alone. However, depression could also be an OSA epiphenomenon such as mood disorder secondary to health problems [75]. Possible evidence for this hypothesis stems from studies showing a decrease in depression after a period of CPAP treatment [20,75–82].

Unrecognition of comorbid OSA in a patient with a psychiatric disorder may lead to inappropriate benzodiazepine medications [83]. While benzodiazepines are commonly used to treat anxiety and sleep problems and in initial depressive treatment, they may cause more apneas or hypopneas as they are decreasing muscle tonus [45], which may be detrimental to OSA patients [79,84]. In addition, daily fatigue and anxiety go hand in hand in patients with OSA [36].

3.2. Anxiety in OSA patients

In the review of contemporary literature, Diaz and Brown [85] note that interaction between anxiety and OSA is unclear and more primary research to uncover true nature of the connection is needed. Furthermore, they state that severity of OSA does not appear to be associated with subjectively reported sleepiness and fatigue, whereas physiological manifestations of anxiety are associated with the severity of subjective symptoms reported. Also, the review suggests that women are more likely to have comorbid OSA and anxiety disorder than man [85]. Studies suggest that underlying neurobiological mechanisms are different in anxiety and depression disorders, thus further supporting evidence that there is difference between comorbid anxious disorders and depressive disorder in patients with OSA [86,87]. Of note, one study shows that treatment with CPAP had a positive effect on anxiety [86]. The review of Gold examines the studies supporting association between anxiety disorders, functional somatic syndromes, and the upper airway dysfunction during wakefulness and sleep [88]. According the author sleep disordered breathing is related to functional somatic syndromes and anxiety disorders through enduring activation of the hypothalamic–pituitary–adrenal axis.

3.3. Cognitive dysfunctions in patients with OSA

Many studies have examined the cognitive functions of OSA patients. A recent meta-review evaluated neuro-cognitive functions in OSA patients using systematic reviews and other meta-analyses [41]. The studies showed that attention, working memory, episodic memory, and executive functions are decreased in OSA [15,89–95]. Conversely, most of the verbal functions remain intact [94,96–103], with mixed results found in psychomotor speed [104]. Different regions of the brain are involved in cognition processes, best studied are frontal cortex and hippocampus. It is noteworthy that male patients with OSA have slower cognitive function decline [105,106]. Macey et al. [107], examined 66 newly diagnosed OSA patients to find significant changes in volume of hippocampal subiculum, more expressed in male population – where the changes were bilateral. Unlike in males, female OSA patients showed volume decreases in the right hippocampus head and tail. Author concludes, that the hippocampus shows sex-specific, OSA-related volume differences, which may contribute to sex-related expression of symptoms in the sleep disorder. Volume increases suggest inflammation and glial activation, whereas volume decreases suggest long-lasting neuronal injury; both pathologic finding may contribute to cognitive dysfunction in OSA.

In the paper by Polsek et al. [108], the authors suggest that prolonged neuronal activation present both in Alzheimer's disease and OSA could be underlying pathophysiological concept accelerating onset of both OSA and Alzheimer's disease, but further research is needed to prove this concept. Also, authors discuss the problematics of compliance with PAP treatment in patients with dementia.

Alchantis et al. [109], found significant changes in frontal cortex of subjects with sleep disordered breathing in an MRI study of OSA patients (22 individuals) in comparison to 10 healthy controls. The authors found that repetitive hypoxemia can promote axonal loss or dysfunction and those changes might be partly irreversible despite of effective CPAP treatment.

3.3.1. Attention

Attention has several characteristics (ie, selectivity, sustainability, and distribution). Selective attention makes it possible to incite or ignore stimuli according to their subjective meaning, mental concentration (sustainability) includes awareness and susceptibility to stimuli over a more extended period; and shifting (distribution) allows to accomplish several tasks simultaneously [99]. Several studies have shown that patients with OSA exhibit deficits in all three parts of attention [41,90,100]. In situations requiring divided attention, such as driving in the simulator when performing another mental assignment, OSA individuals have increased the time to response and more off-road events compared to control subjects [100]. Due to the magnitude and distribution of these deficits, alertness and attention may seem to affect other cognitive functions [95,96,106,110].

Regarding the cognitive decline treatment, an overview of cognitive changes associated with CPAP treatment revealed that 11 of 17 studies demonstrated significant improvement in alertness and attention [97]. However, CPAP is usually not able to return the quality of attention to normal levels. According to research by Lau et al. [111], patients after three months of treatment on CPAP differ from healthy controls in selective and distributed attention. These findings suggest that attention impairment may be partly due to hypoxemia and sleep fragmentation, but OSA is likely to cause a persistent deficiency in the areas of the brain involved in the attention process [93,97,107,111].

3.3.2. Executive functions

Executive functions are a set of different cognitive abilities, such as mental flexibility, behavioral inhibition, working memory, the theory of reasoning and problem-solving. They allow individuals to use their abilities (such as memory, language, visual imagination) adaptively to effectively work in a changing environment [102]. A contemporary meta-analysis showed that OSA patients have impairment in all five sub-domains (eg, in inhibiting, shifting, updating/monitoring information in working memory, generating new knowledge, in verbal fluency, and problem-solving) [110].

Inhibition (ie, the ability to stop an automatic or ongoing response to an event) is critical to cognitive tests such as Stroop's test or Go-No-Go tasks. In these tests, OSA patients make multiple mistakes or have longer reaction times compared to healthy controls [95,96]. In patients with mild to severe OSA, more impulsive errors were found in the maze test [88].

3.3.3. Mental flexibility

Moving the attention or mental flexibility is the ability to move from one cognitive or behavioral approach to another. In Wisconsin's screening test, patients with OSA exhibited increased perseverance compared to healthy subjects [97,110]. Decreased mental flexibility has also been documented in studies using Trail making test B and Zimmermann-Fimm Computer Testing Battery, where OSA patients required a longer time to complete tasks than healthy controls [91,97,110].

3.3.4. Working memory

Working memory is an essential part of cognitive functions, defined as the ability to store, use, update, and track task scope information [113]. Moreover, it was found that patients with OSA managed tasks much worse when compared to healthy controls [97,111]. Redline et al. [114], found that working memory is one of the most frequently diminished parts of executive functions in patients with OSA.

3.3.5. Episodic memory

Similarly, episodic memory was extensively investigated in patients with OSA. Episodic memory is the ability to remember verbal or visual information in a space-time frame. Tasks usually include immediate recall, total recall for multiple steps or learning, delayed recall, and memory recollection. Learning and the ability to remember a list of words, such as the Rey's Hearing-Verbal Test and the California Verbal Test, are examples of episodic memory tests. A recent meta-analysis stated that OSA patients have a different pattern of verbal and visual episodic memory deficits. With word material, each memory component was compromised either immediately or later in delayed recall, learning, or recognition [115]. However, in visuospatial tasks, patients with OSA experienced a worsening only for immediate and delayed recovery, and learning outcomes and recognition were normal [115]. It has been proposed that this deficiency cannot be attributed entirely to the reduced attention or severity of OSA.

3.3.6. Problem-solving

It has also been found that problem-solving, including the assessment and selection of the order of activities to achieve the goal, was also impaired in patients with OSA. In the tests usually used to evaluate this factor of cognitive functions, namely the Tower Test, Naëgelé et al. [116], have shown that patients with OSA need more steps to resolve specific problems. Some executive features of verbal behavior such as mental processing speed, flexibility and synthetic skills are also reduced in OSA patients, regardless of otherwise normal language skills [87,93,116].

In short, investigations have found deficits in most executive functions in patients with OSA, namely reduced processing speed, increased perseverance, impulsivity, and prolonged problem-solving. However, it is important to mention that the studies are significantly heterogeneous in the findings. That may be partly due to sample heterogeneity (with regards to education and/or age), different OSA severity, and the use of various tests [110].

3.3.7. Motoric dysfunctions

Tasks involving fine coordination and psychomotor speed are typically used to investigate motor dysfunctions that arise in the background of the untouched ability of normal movement. In the Purdue Pegboard Test, a drop in manual skills was described in OSA patients [89,116]. Good motor coordination is more sensitive to chronic hypoxemia than fragmentation of sleep [97]. From a literature review, half of the published studies described that OSA patients had reduced processing speeds compared to healthy controls [41]. This limited processing of information is likely to affect performance in some cognitive tests, such as tasks that evaluate executive functions (ie, Tower test or Trail test B) and visual attention. It is no wonder that individuals with OSA had worse outcomes than controls on all tasks that included visuomotor coordination [97].

3.4. Impact of treatment with CPAP on psychiatric comorbidity

There are several articles that show improvement of some psychological disturbances (such as depressive symptoms and partially also cognitive dysfunction) by OSA treatment. CPAP treatment produces small to moderate improvements in executive functions [97,108]. One study, for example, showed improvement in Trail Making Test B and verbal fluency (semantic) in OSA after short CPAP treatment (15 days). Long-term treatment (four months) may not bring any further improvement in cognitive performance tests [117]. In this study, behavioral inhibition and working memory did not change after short (15 days) or long (four months) CPAP treatment [86]. Additionally, it was found that the psychological flexibility of OSA patients did not reach a level of controls after three months of treatment [111]. According the Barnes et al. [118], both CPAP and mandibular advancement decrease successfully treated sleep-disordered breathing and tiredness, but the expected response in neurobehavioral function was partial. In summary, these studies suggest that after a short CPAP treatment, only a particular aspect of the executive functions is recovered, without systematically achieving the level of controls [92,109]. In the neuroimaging study of Rosenzweig et al. [119], patients with OSA underwent one month of PAP treatment. Results suggest that the PAP treatment can lead to adaptive alterations in the neurocognitive architecture and authors suggest that PAP treatment can lead to partial neural recovery. The fact that other cognitive functions such as attention and vigilance are needed to address most cognitive tasks and that OSA can cause permanent damage to the prefrontal cortex could explain some of the mismatches in studies examining the effects of CPAP treatment on cognitive functions [111,120].

In contrast to other cognitive areas, psychomotor speed and fine coordination do not significantly improve after CPAP treatment, indicating that OSA can cause permanent damage to cortical and subcortical regions involved in motor skills [121]. In the CPAP treatment outline, improvement in memory was recorded in approximately half of the examinations [96]. Although all of the components evaluated in OSA's verbal episodic memory are affected, three-month CPAP treatment led to normalization of immediate and delayed recollection and verbal and visual-space learning [41,93,109]. Another important issue is the compliance with treatment, which is in the most studies defined as PAP usage >4 h/night, but this aspect is usually not considered.

4. Discussion

Our review article points out that patients with OSA can also suffer from additional problems, particularly higher depression and anxiety scores and diminished cognitive functions. It is essential to differentiate whether the depression score is connected to the OSA itself, or whether it rather is a manifestation of a comorbid depression disorder. Numerous findings concerning the psychiatric problems in OSA patients have been reported, however, their importance needs to be explored further, as symptoms of OSA partially overlap with mental disorders, especially with the depression disorder. If patients develop depressive disorder, their compliance with the treatment of OSA might be significantly compromised. Furthermore, there is a further decline in quality of life, which is already influenced by OSA itself. The typical symptoms of depression, including depressed mood, sadness or emotional numbness, anhedonia, hypobulia, loss of appetite, depressive thoughts, as well as other symptoms, particularly those that do not respond to CPAP treatment, like hypoprosexia, tiredness and sleep disturbance, can be symptoms of a comorbid depression disorder. There is a need for additional studies that would investigate the comorbid depression by focusing on the core symptoms of depression, while eliminating the symptoms attributable to both depression and OSA – tiredness, sleep disturbance and dysconcentration. The CPAP treatment aimed to reduce the apneic pauses improves the joint symptoms, but it is unknown, whether it would improve the specific symptoms of depressive disorder as well.

Further knowledge in this matter could help to differentiate the patients that would benefit from adjuvant antidepressant treatment from the patients that are to be treated only by the CPAP or surgery.

As sleep related breathing disorders show increased prevalence in mood disorders, we recommend OSA screening in psychiatric patients; because screening will shorten the time needed to make a proper diagnosis [52,54,55,82,121,122], especially when risk factors (eg, male, snoring, obesity etc.) present in patients [52,54,76]. OSA treatment reduces number of apneas/hypopneas and can improve affective symptoms in patients with treatment-resistant depression [53,79–84,123–126].

Contemporary and older studies examining relationship between OSA and cognitive functions show that attention, working memory, episodic memory, and executive functions are decreased in OSA [86–98,127]. In the review from Bucks et al. [120], the authors conducted extensive search of contemporary literature regarding OSA and cognitive functions and state that the evidence is robust for impairment of attention, long term verbal and visual memory and all aspects of executive functioning. More findings suggest that there is also reduced information processing. On the other hand, according to Bucks et al. [120], visuospatial learning and immediate visual recall appears to be intact. Authors found no consistent results in the impairment of short-term memory.

When treated, studies describe that only particular aspect of the executive functions is recovered, without systematically achieving the level of controls [105,109]. Conversely, some parts of cognitive functions such as verbal functions remain intact and some parts of cognitive functions such as psychomotor speed and motoric skills shows mixed results [41,92,95–114,120,128]. Currently, whether this is due to hypoxemia induced damage to different areas of the brain remains unclear and some imaging studies shows that part of the damage from untreated OSA can be irreversible [107–119]. Impairments of cognitive functions need to be evaluated only after the successful treatment of OSA, as they can be mimicked by coincidental loss of concentration due to sleep deprivation. Also, some works suggest that even after period of the treatment with PAP device, cognitive performance in patients with OSA is not at the level of healthy controls [93,111]. This fact further strengthens idea of permanent hypoxemia induced damage to brain in untreated OSA patients. Further research with complex cognitive tests and the focus on changes after treatment is needed to further prove these findings.

The subject is one worthy of review because there is neglect of this connection among psychiatrists, who did not screen the chronic depressed patients for OSA. In addition, the health professionals in sleep disorders, who works with OSA, could overlook the patients with depression and cognitive impairment.

The results mention above have several implications for the practice and future research. There is a strong need in the practice in psychiatry to recognize and monitor OSA, especially in obese patients, patients with the chronic depression, and patient with mild cognitive dysfunction. For the sleep laboratories there is a need for monitoring the mood and cognitive problems in OSA patients. In the future, research should focus more deeply to the recognize distinction between depressive symptoms and symptoms of OSA, constructing more appropriate questionnaires and assessment tools.

The study provide examination of recent or current literature. It covers extensive collection of investigations at various levels of completeness and generality. The strengths of the study are:

- The study summarizes the current state of knowledge and gaps in the topic of psychiatric disorders in OSA patients, without repetition and identifying omission.
- Study selection was described.
- The inclusion and the exclusion criteria were described.
- Article selection was done in duplicate.
- Flow chart of study selection was provided.

The limitations of the study are:

- Meta-analysis was not conducted.
- Is reliant upon the searcher to determine value added that the variety of methods and findings the studies give.

5. Conclusion

OSA is a severe illness that has a high prevalence in the adult population and will most likely continue to increase in the future due to the trend of increasing the average weight. In our conditions, sleep apnea is usually diagnosed too late, and despite repeated observations of typical night-time symptoms in inpatient care, clinicians rarely consider it. Untreated OSA worsens many cardiovascular diseases, prevents their compensation, impacts affective disorders, and often leads to worsening of cognitive functions or even to permanent brain damage. Every patient with chronic depression should be evaluated for OSA and maybe any inspiratory airflow limitation should be treated in these patients [129]. A particular topic for psychiatry is the possibility of developing secondary OSA after the side effect of several psychopharmacs in the form of weight gain. Metabolic syndrome in individuals taking second-generation antipsychotics is thought to be mediated by antipsychotic-induced weight gain. However, recent literature challenges this notion, and theoretically, it may also be mediated through obstructive sleep apnea (OSA) [130]. For the reasons mentioned above, obstructive sleep apnea should be included in the differential diagnosis of both inpatient and outpatient care, especially when the difficulty of achieving quality remission of psychiatric disorder is present. Further studies are needed to examine the connection between OSA and affective disorders, anxiety disorders, and their effect on cognitive functions entirely, especially in the context of CPAP treatment.

Conflict of interest

The authors report no conflicts of interest in this work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.03.017.

References

[1] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136–43.
[2] Eikermann M, Jordan AS, Chamberlin NL, et al. The influence of ageing on pharyngeal collapsibility during sleep. Chest 2007;131(6):1702–9.
[3] Neelapu BC, Kharbanda OP, Sardana HK, et al. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. Sleep Med Rev 2017;31:79–90.
[4] Kubota Y, Nakayama H, Takada T, et al. Facial axis angle as a risk factor for obstructive sleep apnea. Intern Med 2005;44(8):805–10.
[5] Avci S, Lakadamyali H, Lakadamyali H, et al. Relationships among retropalatal airway, pharyngeal length, and craniofacial structures determined by magnetic resonance imaging in patients with obstructive sleep apnea. Sleep Breath 2019;23(1):103–15.
[6] American Academy of Sleep Medicine, American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual. 3rd ed. 2014. Darien, IL, USA.
[7] De Castro RJ, Rosales-Mayor E. Depressive symptoms in patients with obstructive sleep apnea/hypopnea syndrome. Sleep Breath 2013;17:615–20.
[8] Schröder CM, O'Hara R. Depression and obstructive sleep apnea (OSA). Ann Gen Psychiatry 2005;4:13–20.

[9] Deldin PJ, Phillips LK, Thomas RJ. A preliminary study of sleep-disordered breathing in major depressive disorder. Sleep Med 2006;7:131–9.
[10] Kaplan R. Obstructive sleep apnoea and depression – diagnostic and treatment implications. Aust N Z J Psychiatry 1992;26:586–91.
[11] O'Hara R, Schröder CM, Kraemer HC, et al. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. Neurology 2005;65:642–4.
[12] Chen YH, Keller JK, Kang JH, et al. Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. J Clin Sleep Med 2013;9:417–4123.
[13] Saunamäki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2007;116:277–88.
[14] Kim HC, Young T, Matthews CG, et al. Sleep-disordered breathing and neuropsychological deficits. A population-based study. Am J Respir Crit Care Med 1997;156:1813–9.
[15] Aloia MS, Arnedt JT, Smith L, et al. Examining the construct of depression in obstructive sleep apnea syndrome. Sleep Med 2005;6:115–21.
[16] Harris M, Glozier N, Ratnavadivel R, et al. Obstructive sleep apnea and depression. Sleep Med Rev 2009;13:437–44.
[17] Ejaz SM, Khawaja IS, Bhatia S, et al. Obstructive sleep apnea and depression: a review. Innov Clin Neurosci 2011;8:17–25.
[18] Smith R, Ronald J, Delaive K, et al. What are obstructive sleep apnea patients being treated for prior to this diagnosis? Chest 2002;121:164–72.
[19] Stores G. Misdiagnosing sleep disorders as primary psychiatric conditions. Adv Psychiatr Treat 2003;9:69–77.
[20] Borak J, Cieslicki J, Szelenberger W, et al. Psychopathological characteristics of the consequences of obstructive sleep apnea before and three months after CPAP. Psychiatr Pol 1994;28:33–44.
[21] Turnbull CD, Wang SH, Manuel AR, et al. Relationships between MRI fat distributions and sleep apnea and obesity hypoventilation syndrome in very obese patients. Sleep Breath 2018;22(3):673–81.
[22] Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med 2000;160(15):2289–95.
[23] Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31(8):1071–8.
[24] Pombo N, Garcia N, Bousson K. Classification techniques on computerized systems to predict and/or to detect apnea: a systematic review. Comput Methods Programs Biomed 2017;140:265–74.
[25] Pelletier-Fleury N, Meslier N, Gagnadoux F, et al. Economic arguments for the immediate management of moderate-to-severe obstructive sleep apnoea syndrome. Eur Respir J 2004;23(1):53–60.
[26] Peppard PE, Szklo-Coxe M, Hla KM, et al. Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med 2006;166:1709–15.
[27] Sonka K, Kelemen J, Kemlink D, et al. Evening and morning plasma levels of protein S100B in patients with obstructive sleep apnea. Neuro Endocrinol Lett 2007;28(5):575–9.
[28] Somers VK, White DP, Amin R, et al., American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, American Heart Association Stroke Council, American Heart Association Council on Cardiovascular Nursing, American College of Cardiology Foundation. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118(10):1080–111.
[29] Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity. Arch Intern Med 2003;163:2058–65.
[30] Rodsutti J, Hensley M, Thakkinstian A, et al. A clinical decision rule to prioritize polysomnography in patients with suspected sleep apnea. Sleep 2004;27(4):694–9.
[31] Povitz M, Bolo CE, Heitman SJ, et al. Effect of treatment of obstructive sleep apnea on depressive symptoms: systematic review and meta-analysis. PLoS Med 2014;11(11):e1001762.
[32] BaHammam AS, Kendzerska T, Gupta R, et al. Comorbid depression in obstructive sleep apnea: an under-recognized association. Sleep Breath 2016;20(2):447–56.
[33] Hobzova M, Hubackova L, Vanek J, et al. Cognitive function and depressivity before and after cpap treatment in obstructive sleep apnea patients. Neuro Endocrinol Lett 2017;38(3):145–53.
[34] Pamidi S, Knutson KL, Ghods F, et al. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. Sleep Med 2011;12(9):827–31.
[35] Wiersema C, Van Zelst W, Oude Voshaar R. When a patient with depression is feeling sleepy, be aware of sleep apnoea. BMJ Case Rep 2018;2018. pii: bcr-2018-224873.
[36] Bardwell WA, Ancoli-Israel S, Dimsdale JE. Comparison of the effects of depressive symptoms and apnea severity on fatigue in patients with obstructive sleep apnea: a replication study. J Affect Disord 2007;97(1–3):181–6.
[37] Amdo T, Hasaneen N, Gold MS, et al. Somatic syndromes, insomnia, anxiety, and stress among sleep disordered breathing patients. Sleep Breath 2016;20(2):759–68.
[38] Bao YP, Han Y, Ma J, et al. Co-occurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review. Neurosci Biobehav Rev 2017;75:257–73.
[39] Bjorvatn B, Rajakulendren N, Lehmann S, et al. Increased severity of obstructive sleep apnea is associated with less anxiety and depression. J Sleep Res 2017. https://doi.org/10.1111/jsr.12647 [Epub ahead of print].
[40] Hobzova M, Prasko J, Vanek J, et al. Depression and obstructive sleep apnea. Neuro Endocrinol Lett 2017;38(5):343–52.
[41] Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. Respirology 2013;18:61–70.
[42] Argun Baris S, Tuncel D, Ozerdem C, et al. The effect of positive airway pressure therapy on neurocognitive functions, depression, and anxiety in obesity hypoventilation syndrome. Multidiscip Respir Med 2016;11:35. PMID: 27766147.
[43] Bhat S, Gupta D, Akel O, et al. The relationships between improvements in daytime sleepiness, fatigue and depression and psychomotor vigilance task testing with CPAP use in patients with obstructive sleep apnea. Sleep Med 2018;49:81–9.
[44] Bucks RS, Nanthakumar S, Starkstein SS, et al. Discerning depressive symptoms in patients with obstructive sleep apnea: the effect of continuous positive airway pressure therapy on Hamilton Depression Rating Scale symptoms. Sleep 2018;41(12). https://doi.org/10.1093/sleep/zsy178. PubMed PMID: 30203079.
[45] Cheng P, Casement MD, Chen C, et al. Breathing and depression sleep-disordered breathing in major depressive disorder. J Sleep Res 2013;22:459–62.
[46] Moher D, Liberati A, Tetzlaff J, et al., The PRISMA Group. Methods of systematic reviews and meta-analysis preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. J Clin Epidemiol 2009;62:1006e1012.
[47] Senaratna CV, English DR, Currier D, et al. Sleep apnoea in Australian men: disease burden, co-morbidities, and correlates from the Australian longitudinal study on male health. BMC Public Health 2016;16(Suppl 3):1029. https://doi.org/10.1186/s12889-016-3703-8.
[48] Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems, and stress responsivity. Sleep Med Rev 2008;12:197–201.
[49] Gupta MA, Simpson FC. Obstructive sleep apnea and psychiatric disorders: a systematic review. J Clin Sleep Med 2015;11:165–75.
[50] Kang J, Tian Z, Li M. Changes in insular cortex metabolites in patients with obstructive sleep apnea syndrome. Neuroreport 2018 Aug 15;29(12):981–6.
[51] Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci 2008;10:473–81.
[52] Ong JC, Gress JL, Pedro-Salcedo MG, et al. Frequency and predictors of obstructive sleep apnea among individuals with major depressive disorder and insomnia. J Psychosom Res 2009;67(2):135–41.
[53] Nasr S, Wendt B, Kora S. Increased incidence of sleep apnea in psychiatric outpatients. Ann Clin Psychiatry 2010;22:29–32.
[54] Hattori M, Kitajima T, Mekata T, et al. Risk factors for obstructive sleep apnea syndrome screening in mood disorder patients. Psychiatry Clin Neurosci 2009;63:385–91.
[55] Pan ML, Tsao HM, Hsu CC, et al. Bidirectional association between obstructive sleep apnea and depression: a population-based longitudinal study. Medicine 2016;95:e4833.
[56] Lee S. Depression in sleep apnea: a different view. J Clin Psychiatry 1990;51:309–10.
[57] Gall R, Isaac L. Quality of life in mild sleep apnea. Sleep 1993;16(Suppl):S59–61.
[58] Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. J Allergy Clin Immunol 1997;99(Suppl):S750–6.
[59] Klonoff H, Fleetham J, Taylor DR, et al. Treatment outcome of obstructive sleep apnea: physiological and neuropsychological concomitants. J Nerv Ment Dis 1987;175:208–12.
[60] Bardwell WA, Berry CC, Ancoli-Israel S, et al. Psychological correlates of sleep apnea. J Psychosom Res 1999;47:583–96.
[61] Pillar G, Lavie P. Psychiatric symptoms in sleep apnea syndrome: effects of gender and respiratory disturbances index. Chest 1998;114:697–703.
[62] Cheshire K, Engleman H, Deary I, et al. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992;152:538–41.
[63] Platon MJ, Sierra JE. Changes in psychopathological symptoms in sleep apnea patients after treatment with nasal continuous positive airway pressure. Int J Neurosci 1992;62:173–95.
[64] Edinger J, Carwile S, Miller P, et al. Psychological status, syndromatic measures, and compliance with nasal CPAP therapy for sleep apnea. Percept Mot Skills 1994;78:1116–8.
[65] Engleman HM, Martin SE, Deary IJ, et al. Effect of continuous positive airway pressure treatment on daytime functioning in sleep apnea/hypopnea syndrome. Lancet 1994;343:572–5.
[66] Aikens JE, Mendelson WB. A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. Sleep 1999;22:355–9.

[67] Goldstein LT, Goldsmith SJ, Anger K, et al. Psychiatric symptoms in clients presenting for commercial weight reduction treatment. Int J Eat Disord 1996;20(2):191–7.
[68] Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54(3):216–26.
[69] Arnau RC, Meagher MW, Norris MP, et al. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychol 2001;20(2):112–9.
[70] Carpenter KM, Hasin DS, Allison DB, et al. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. Am J Public Health 2000;90(2):251.
[71] McNamara SG, Grunstein RR, Sullivan CE. Obstructive sleep apnea. Thorax 1993;48:754–64.
[72] Wang J, Yu W, Gao M, et al. Impact of obstructive sleep apnea syndrome on endothelial function, arterial stiffening, and serum inflammatory markers: an updated meta-analysis and meta-regression of 18 studies. J Am Heart Assoc 2015;4(11):e002454.
[73] Li YY, Mazarakis T, Shen YC, et al. Anxiety and depression are improved by continuous positive airway pressure treatments in obstructive sleep apnea. Int J Psychiatry Med 2016;51:554–62.
[74] Smith IE, Shneerson JM. Is the SF 36 sensitive to sleep disruption? A study in subjects with sleep apnea. J Sleep Res 1995;4:183–8.
[75] Means MK, Lichstein KL, Edinger JD, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. Sleep Breath 2003;7(1):31–42.
[76] Rawdin BJ, Mellon SH, Dhabhar FS, et al. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav Immun 2013;31:143–52.
[77] Cassel W. Sleep apnea and personality. Sleep 1993;16:S56–8.
[78] Adams RJ, Appleton SL, Vakulin A, et al. Association of daytime sleepiness with obstructive sleep apnoea and comorbidities varies by sleepiness definition in a population cohort of men. Respirology 2016;21(7):1314–21.
[79] Sánchez AI, Buela-Casal G, Bermudez MP, et al. The effects of continuous positive air pressure treatment on anxiety and depression levels in apnea patients. Psychiatry Clin Neurosci 2001;55(6):641–6.
[80] McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. World Med J 2003;102:36–43.
[81] Habukawa M, Uchimura N, Kakuma T, et al. Effect of CPAP treatment on residual depressive symptoms in patients with major depression and coexisting sleep apnea: contribution of daytime sleepiness to residual depressive symptoms. Sleep Med 2010;11(6):552–7.
[82] Edwards C, Mukherjee S, Simpson L, et al. Depressive symptoms before and after treatment of obstructive sleep apnea in men and women. J Clin Sleep Med 2015;11(9):1029–38.
[83] Jacobsen JH, Shi L, Mokhlesi B. Factors associated with excessive daytime sleepiness in patients with severe obstructive sleep apnea. Sleep Breath 2013;17(2):629–35.
[84] Hrubos-Strøm H, Einvik G, Nordhus IH, et al. Sleep apnoea, anxiety, depression and somatoform pain: a community-based high-risk sample. Eur Respir J 2012;40:400–7.
[85] Diaz SV, Brown LK. Relationships between obstructive sleep apnea and anxiety. Curr Opin Pulm Med 2016;22(6):563–9.
[86] Lee MC, Shen YC, Wang JH, et al. Effects of continuous positive airway pressure on anxiety, depression, and major cardiac and cerebro-vascular events in obstructive sleep apnea patients with and without coronary artery disease. Ci Ji Yi Xue Za Zhi 2017;29(4):218–22.
[87] Nutt DJ, Stein DJ. Understanding the neurobiology of comorbidity in anxiety disorders. CNS Spectr 2006;11(S12):13–20.
[88] Gold AR. Functional somatic syndromes, anxiety disorders and the upper airway: a matter of paradigms. Sleep Med Rev 2011;15(6):389–401.
[89] Bedard MA, Montplaisir J, Richer F, et al. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. Chest 1991;100:367–70.
[90] Decary A, Rouleau I, Montplaisir J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 2000;23:369–81.
[91] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11:1–16.
[92] Rouleau I, Decary A, Chicoine AJ, et al. Procedural skill learning in obstructive sleep apnea syndrome. Sleep 2002;25:401–11.
[93] Salorio CF, White DA, Piccirillo J, et al. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. J Clin Exp Neuropsychol 2002;24:93–100.
[94] Ferini-Strambi L, Baietto C, Di Gioia MR, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003;61(1):87–92.
[95] Verstraeten E, Cluydts R, Pevernagie D, et al. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. Sleep 2004;27:685–93.
[96] Naëgelé B, Pepin JL, Levy P, et al. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 1998;21:392–7.
[97] Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. Sleep Med Rev 2004;8:257–67.
[98] Barkley RA. Behavioural inhibition sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121:65–94.
[99] Aloia MS, Arnedt TJ, Davis JD, et al. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc 2004;10:772–85.
[100] Lezak M, Howieson D, Loring D. Neuropsychological assessment. 4th ed. Oxford University Press; 2004.
[101] Sforza E, Haba-Rubio J, De Bilbao F, et al. Performance vigilance task and sleepiness in patients with sleep-disordered breathing. Eur Respir J 2004;24:279–85.
[102] Mazza S, Pepin JL, Naegele B, et al. Most obstructive sleep apnoea patients exhibit vigilance and attention deficits on an extended battery of tests. Eur Respir J 2005;25:75–80.
[103] Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev 2006;16:17–42.
[104] Kilpinen R, Saunamaki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2014;129:209–18.
[105] Shpirer I, Elizur A, Shorer R, et al. Hypoxemia correlates with attentional dysfunction in patients with obstructive sleep apnea. Sleep Breath 2012;16(3):821–7.
[106] Grigg-Damberger M, Ralls F. Cognitive dysfunction and obstructive sleep apnea: from cradle to tomb. Curr Opin Pulm Med 2012 Nov;18(6):580–7.
[107] Macey PM, Prasad JP, Ogren JA, et al. Sex-specific hippocampus volume changes in obstructive sleep apnea. Neuroimage Clin 2018;20:305–17.
[108] Polsek D, Gildeh N, Cash D, et al. Obstructive sleep apnoea and Alzheimer's disease: in search of shared pathomechanisms. Neurosci Biobehav Rev 2018;86:142–9.
[109] Alchantis M, Deligiorgis N, Zias N, et al. Frontal brain lobe impairment in obstructive sleep apnoea: a proton MR spectroscopy study. Eur Respir J 2004;24:980–6.
[110] Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. Sleep 2013;36:1297–305.
[111] Lau EY, Eskes GA, Morrison DL, et al. Executive function in patients with obstructive sleep apnea treated with continuous positive airway pressure. J Int Neuropsychol Soc 2010;16:1077–88.
[112] Redline S, Tishler PV, Hans MG, et al. Racial difference in sleep disordered breathing in African Americans and Caucasians. Am J Respir Crit Care Med 1997;155:186–92.
[113] Miyake A, Shah P. Models of working memory: mechanisms of active maintenance and executive control. United Kingdom: Cambridge University Press; 1999.
[114] Redline S, Budhiraja R, Kapur V, et al. The scoring of respiratory events in sleep: reliability and validity. J Clin Sleep Med 2007;3(2):169–200.
[115] Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. Sleep 2013;36:203–20.
[116] Naëgelé B, Thouvard V, Pépin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;18(1):43–52.
[117] Loredo JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure vs placebo continuous positive airway pressure on sleep quality in obstructive sleep apnea. Chest 1999;116:1545–9.
[118] Barnes M, McEvoy RD, Banks S, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170(6):656–64.
[119] Rosenzweig I, Glasser M, Crum WR, et al. Changes in neurocognitive architecture in patients with obstructive sleep apnea treated with continuous positive airway pressure. EBioMedicine 2016;7:221–9.
[120] Bucks RS, Olaithe M, Rosenzweig I, et al. Reviewing the relationship between OSA and cognition: where do we go from here? Respirology 2017;22(7):1253–61.
[121] Wheaton AG, Perry GS, Chapman DP, et al. Sleep disordered breathing and depression among U.S. adults: National Health and Nutrition Examination Survey, 2005-2008. Sleep 2012;35:461–7.
[122] Stubbs B, Vancampfort D, Veronese N, et al. The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: a systematic review and meta-analysis. J Affect Disord 2016;197:259–67.
[123] Diamanti C, Manali E, Ginieri-Coccossis M, et al. Depression, physical activity, energy consumption, and quality of life in OSA patients before and after CPAP treatment. Sleep Breath 2013;17:1159–68.
[124] Yamamoto H, Akashiba T, Kosaka N, et al. Long-term effects nasal continuous positive airway pressure on daytime sleepiness, mood and traffic accidents in patients with obstructive sleep apnoea. Respir Med 2000;94:87–90.
[125] Joseph S, Zuriqat M, Husari A. Sustained improvement in cognitive and emotional status of apneic patients after prolonged treatment with positive airway pressure. South Med J 2009;102:589–94.

[126] Mathieu A, Mazza S, Décary A, et al. Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. Sleep Med 2008;9(2):112–20.
[127] Tulek B, Atalay NB, Kanat F, et al. Attentional control is partially impaired in obstructive sleep apnea syndrome. J Sleep Res 2013;22:1–8.
[128] Miller P, Iyer M, Gold AR. Treatment resistant adolescent depression with upper airway resistance syndrome treated with rapid palatal expansion: a case report. J Med Case Rep 2012;6:415.
[129] Rohatgi R, Gupta R, Ray R, et al. Is obstructive sleep apnea the missing link between metabolic syndrome and second-generation antipsychotics: preliminary study. Indian J Psychiatry 2018;60(4):478–84.
[130] Macey PM, Woo MA, Kumar R, et al. Relationship between obstructive sleep apnea severity and sleep, depression and anxiety symptoms in newly-diagnosed patients. PLoS One 2010;5:e10211.