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Cognition in Obstructive Sleep Apnea-Hypopnea Syndrome (OSAS): Current Clinical Knowledge and the Impact of Treatment

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Abstract

Obstructive sleep apnea-hypopnea syndrome (OSAS) is characterized by the presence of disordered breathing events that occur during sleep, as well as symptoms such as sleepiness and snoring. OSAS is associated with a number of adverse health consequences, and a growing literature focuses on its cognitive correlates. Although research in this field is mixed, multiple studies indicate that OSAS patients show impairment in attention, memory, and executive function. Continuous positive airway pressure (CPAP) is the most effective and widely used treatment of OSAS, and supplemental medications may supplement CPAP treatment to ameliorate associated symptoms. Here we review the literature on OSAS and cognition, including studies that have investigated the impact of CPAP and stimulant medication on cognitive performance in patients with OSAS. In general, no consistent effect of CPAP use on cognitive performance was evident. This may be due, in part, to variability in study design and sampling methodology across studies. Studies of stimulant medications generally reported positive effects on cognitive performance. We conclude with a discussion of the mechanisms that have been proposed to explain cognitive dysfunction in OSAS and directions for future research.

Keywords

obstructive sleep apnea; cognition; CPAP; stimulant

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAS) is a respiratory sleep disorder that is caused by a blockage or narrowing of the upper airway (Cao, 2005). In OSAS, sleep often becomes fragmented due to repeated respiratory events, which are identified as *apneas* when airflow is stopped for ten or more seconds, or *hypopneas* when airflow decreases by 30% or more and is accompanied by a decrease in oxyhemoglobin saturation (Iber, 2007). Diagnosis of OSAS is based on summary indices of respiratory events, such as the apnea-hypopnea index (AHI; mean number of apneas + hypopneas per hour of sleep) or the respiratory disturbance index (RDI; mean number of apneas + hypopneas + respiratory effort-related arousals per hour of sleep) (Redline, 2000). In general, an AHI of 5-15 constitutes mild

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OSAS, 16-30 is considered moderate, and greater than 30 is severe (Iber, 2007). The hallmark symptom of OSAS is excessive daytime sleepiness, although patients commonly experience repeated awakenings from sleep, feelings of choking or gasping, snoring, flailing or thrashing during sleep, decreased capacity for concentration, and impaired functioning in daily activities (Cao, 2005).

Deteriorations in quality of life (Finn, 1998) and affect, which can include irritability, depression, and anxiety (Sharafkhaneh, 2005) are common among patients with OSAS. Fortunately, effective treatment is available for OSAS. The most consistently effective treatment is continuous positive airway pressure (CPAP), which uses a mask to deliver a calibrated level of pressure to keep the airway open, thus significantly eliminating or attenuating the occurrence of apneas and hypopneas (Atwood, 2005). Alternate treatment techniques, including oral appliances, surgery, or weight loss (Grunstein, 2007), may be prescribed in circumstances where CPAP is not well tolerated or is otherwise insufficient for treating OSAS. Additionally, when CPAP treatment does not sufficiently improve daytime sleepiness, pharmacological interventions may supplement standard CPAP regimens in order to ameliorate the excessive sleepiness and fatigue (Atwood, 2005).

A growing literature ties OSAS to a range of adverse health outcomes, including all-cause mortality (Yaggi, 2005; Marshall, 2008; Young, 2008) and morbidity due to stroke (Yaggi, 2005), cardiovascular disease (Peker, 2002; Pepperell, 2011), hypertension (Carlson, 1994; Drager, 2010), and insulin resistance (Ip, 2002; Babu, 2005). Individuals with OSAS are also more likely to be involved in both fatal and non-fatal motor vehicle accidents (Findley, 1988; Masa, 2000; Hiestand, 2011). Medical costs, combined with functional losses, frequently place a significant financial burden upon patients with OSAS, which in turn places economic strain upon the entire national healthcare system (Kapoor, 2010).

Among the most prominent adverse consequences associated with OSAS is impairment in cognitive functioning, which is observed in many OSAS patients (Greenberg, 1987; Aloia, 2004). This consequence is of particular concern, given its implications for work performance, social functioning, and everyday activity. In this paper, we discuss previous research and the current understanding of cognition in OSAS; we continue this discussion with a review of empirical work that has investigated the impact of both standard and supplemental treatment interventions on cognitive performance. We then discuss several methodological issues present within the existing literature and the implications of these findings for future research.

Epidemiologic Factors

The prevalence of OSAS is estimated to be 4% for middle-aged American men and 2% for middle-aged American women (Young, 1993). Males are at a significantly higher risk for developing OSAS than females (Bixler, 2001). Age is another significant risk factor for OSAS, as incidence increases steadily with age for both men and women (Ancoli-Israel, 1991; Young, 1993; Bixler, 1998). Research also suggests that the burden of OSAS and its associated symptoms is greater within racial and ethnic minority groups when compared to White groups (Ancoli-Israel, 1995; Redline, 1997; O'Connor, 2003; Fiorentino, 2006).

Prevalence estimates of OSAS vary across studies based on research design and sampling criteria (Redline, 2000). The American Academy of Sleep Medicine (AASM) defines OSAS as AHI ≥ 5 plus the presence of two or more symptoms, such as daytime sleepiness or snoring (American Academy of Sleep Medicine Task Force, 1999). Many researchers hypothesize that a large proportion of the general population may suffer from an elevated AHI, but does not experience any associated symptoms (Young, 1997). For example, in a representative sample of U.S. men, the prevalence of OSAS (defined by AHI > 10 and the

presence of daytime symptoms) was 3.3%, while the prevalence of any AHI > 5 was 17%, indicating that many individuals endure respiratory events but may not experience, or report, the symptoms of OSAS (Bixler, 1998). Similarly, Young and colleagues (1993) reported that 9% of women and 24% of men had an AHI > 5, but were asymptomatic for OSAS. Thus, current prevalence estimates of OSAS do not capture everyone suffering from sleep-disordered breathing. In one representative sample, one in four U.S. adults was identified as being at high risk for OSAS (Hiestand, 2006).

Cognitive Impairment Associated with OSAS

Although the extent of cognitive dysfunction in OSAS is not fully understood (Quan, 2006; Sforza, 2010; Quan, 2011), several prior reviews of the literature suggested that OSAS patients exhibit significant impairment on neuropsychological tests (Décary, 2000; Sateia, 2003; Aloia, 2004; El-Ad, 2005). Authors who have previously reviewed the evidence on OSAS and cognition have categorized cognition into four discrete (although not mutually exclusive) domains: intellectual function, memory, attention, and executive function (Décary, 2000; Sateia, 2003). We follow the same categorization scheme in our review of the current literature.

Relatively little research has specifically examined the influence of OSAS on intellectual function. Deficits in measures of global intellectual function have been reported by individual studies (Findley, 1986; Greenberg, 1987; Bédard, 1991). However, a meta-analysis of twenty-five studies reported no significant impairment in intellectual function in OSAS patients compared to control subjects and normative data (Beebe, 2003). One study reported that OSAS patients with intellectual function scores in the 90th percentile maintained normative attentional capacity, which suggests that high intellectual function may protect against the deterioration of some other cognitive abilities in OSAS (Alchanatis, 2005).

More commonly, researchers have investigated whether OSAS has an impact within the domain of memory. Although several individual studies have suggested that OSAS patients experience impairments in both short-term and long-term memory (Bédard, 1991; Naëgelé, 1995; Salorio, 2002; Bawden, 2011), these findings were not supported by a meta-analysis (Beebe, 2003). More recent work suggests that OSAS patients perform significantly worse on tests of verbal memory, but not visual memory, when compared to controls (Kloepfer, 2009; Twigg, 2010). Taken together, this literature suggests that individuals with OSAS may exhibit impairments in some aspects of memory.

The observation that OSAS patients are at increased risk for motor vehicle accidents (Terán-Santos, 1999; Masa, 2000) has spurred investigation of cognitive capacities in OSAS, especially relative to the processes of attention. Driving simulation instruments are designed to mimic real-world driving conditions, and therefore measure the reaction time and sustained attention of subjects (Pichel, 2006). Individuals with OSAS have consistently exhibited worse performance in these simulations compared to controls (Findley, 1988; George, 1996; Juniper, 2000; Tippin, 2009). Differences between OSAS patients and controls have been shown on more traditional neuropsychological tests of attention, (Mazza, 2005; Bawden, 2011; Shpirer, 2011) and these findings were corroborated by the results of a meta-analysis (Beebe, 2003).

A fourth cognitive domain, executive function, refers to the higher order cognitive processes including problem-solving, judgment, inhibition and set switching, and cognitive flexibility (Alvarez, 2006). Several studies have suggested that executive function may be significantly impacted by OSAS (Lis, 2008; Bawden, 2011). One systematic review posited that executive function may be the cognitive domain most impaired in OSAS (Saunamäki,

2007). Specifically, patients show impairment on tests that require set shifting, mental flexibility, and planning (Saunamäki, 2009). Other authors have reported disturbances in some, but not all, measures of executive function in OSAS patients (Salorio, 2002). Despite mixed results, the bulk of this literature suggests that executive function is impaired to some degree in patients with OSAS.

Effect of CPAP Treatment on Cognition

A question of great clinical and public health relevance is if, and to what extent, the cognitive deficits exhibited by individuals with OSAS may be improved by standard treatment techniques. In the following section, we review empirical studies that have investigated the effect of CPAP treatment on neuropsychological performance in OSAS patients. Studies in this area vary by sample characteristics, methodology, and design, and include traditional randomized controlled trials (RCTs) as well as case-control designs and within-subject studies. There is a dearth of RCTs in this area of research. The randomization of patients to a placebo condition has raised ethical concerns (Karlawish, 2001) as CPAP is well established as the gold-standard treatment for OSAS. Nevertheless, since most OSAS patients have lived with their OSAS for many years before being diagnosed, randomization to up to three weeks of placebo CPAP is often used as it is only with comparisons to placebo that the true effect of CPAP can be established. Nevertheless, many investigators have utilized a randomized crossover design or have simply employed a non-randomized study design. Although previous research has investigated the cognitive effects of CPAP treatment in RCTs (Sanchez, 2009), we chose to consider the wide range of study designs in our review.

The sample characteristics, designs, and main findings from the RCTs of CPAP treatment on cognition are presented in Table 1. Six of these trials reported no significant difference in cognitive performance between the CPAP and control groups following treatment (Engleman, 1998; Lojander, 1999; Monasterio, 2001; Ancoli-Israel, 2008; Gagnadoux, 2009; Vennelle, 2010; Ryan, 2011). On the other hand, seven other trials reported significant differences between these groups following CPAP treatment in the domains of attention (Engleman, 1994; Engleman, 1999; Barbé, 2001; Lim, 2007) and executive function (Engleman, 1994; Engleman, 1997; Engleman, 1999; Barnes, 2002). Other studies reported improved performance in patients from pre-CPAP to post-CPAP in the specific domains of executive function (Henke, 2001; Gagnadoux, 2009) and attention (Henke, 2001; Lim, 2007; Ryan, 2011), as well as on a composite neuropsychological battery (Bardwell, 2001; Ancoli-Israel, 2008).

Significant improvement in cognitive performance following CPAP treatment was reported in studies that utilized a within-subjects design. These studies reported improvements in memory (Aloia, 2003; Joseph, 2009; Zimmerman, 2009), attention (Aloia, 2003), and executive function (Aloia, 2003; Gale, 2004) after three months (Aloia, 2003; Zimmerman, 2006) and six months (Gale, 2004; Joseph, 2009) of follow-up. Studies that utilized a case-control design also reported improvements in OSAS patients treated with CPAP compared to age-matched healthy control subjects. Specifically, cognition improved in areas of memory (Tonon, 2007; Canesesa, 2010), sustained attention (Muñoz, 2000), motor speed, and executive function (Naëgelé, 1998; Ferini-Strambi, 2003).

Three studies investigated cognitive performance after CPAP in individuals with diagnosed neurological conditions, namely patients with mild probable Alzheimer's disease (AD) (Ancoli-Israel, 2008; Cooke, 2009) and patients recovering from recent stroke (Hsu, 2006; Ryan, 2011). An RCT of CPAP treatment in AD reported that, following three weeks of CPAP treatment, general cognitive performance improved within a sample of OSAS patients

with AD although, likely due to insufficient power, no differences in improvement between the CPAP condition and the control condition were observed (Ancoli-Israel, 2008). Follow-up analyses on a subset of this sample suggested that adherent CPAP use might slow cognitive decline, especially in the domain of executive function and processing speed, in AD patients with OSAS (Cooke, 2009). In two RCTs of recent stroke patients, no significant differences in cognitive performance were observed when the CPAP condition was compared to the control (in this case standard rehabilitation) condition (Hsu, 2006; Ryan, 2011), although digit and visual span backwards did improve within the CPAP group following one month of treatment (Ryan, 2011). Taken together, these studies provide some preliminary evidence that AD or stroke patients with sleep-disordered breathing may experience some cognitive benefit from CPAP treatment. Because cognitive impairment related to OSAS is not well understood in these populations, additional RCTs are needed in order to better understand the impact of CPAP on cognition in populations with identified neurologic disease.

One striking feature of studies of CPAP and cognition is the between-study variability in duration of exposure to CPAP treatment. For example, some studies investigated cognitive change after one week of CPAP use (Bardwell, 2001), while others followed subjects for up to 12 months (Muñoz, 2000). Some have argued that no dose-response relationship exists between the length of time on CPAP treatment and the level of cognitive improvement (Valencia-Flores, 1996). This argument is supported by a finding that CPAP use was associated with improved attention, spatial ability, and motor speed in OSAS patients, and these results were the same after 15 days of follow-up as the results after four months (Ferini-Strambi, 2003). Similarly, another study reported that, although cognition improved after three weeks, no differences in performance were observed between three weeks and six weeks of CPAP treatment (Ancoli-Israel, 2008). Significant improvements in cognition were observed after just one week (Bardwell, 2001) and two weeks (Lim, 2007) of CPAP treatment. In an exception to this pattern, one study reported that sustained attention improved in patients compared to controls after 3 months of CPAP treatment and continued to improve following 12 months of treatment (Muñoz, 2000).

Another noticeable source of heterogeneity in this research is differential inclusion and exclusion criteria. Although some studies utilized the AASM guidelines for determining study eligibility, (Engleman, 1993; Engleman, 1997; Engleman, 1998; Engleman, 1999, Engleman, 2002; Ferini-Strambi, 2003; Zimmerman, 2006; Tonon, 2007; Gagnadoux, 2009; Vennelle, 2010), others included subjects based solely on the number of respiratory events that occurred during sleep, regardless of symptom presence (Bardwell, 2001; Barnes, 2002; Lim, 2007; Ryan, 2011). The AHI cut-off used to select subjects also varied across studies; some included participants with an AHI ≤ 5 or AHI ≤ 10 (Muñoz, 2000; Lim, 2007; Cooke, 2009; Joseph, 2009; Saunamäki, 2010), while others included subjects with AHI ≤ 20 (Borak, 1996; Barbé, 2001; Ferini-Strambi, 2003; Canessa, 2010). Few authors chose to utilize the alternative RDI measurement (Aloia, 2003; Lau, 2010) in the evaluation of respiratory events. Because the RDI can be calculated using several methods, this measurement may not always reliably identify the severity of OSAS (Redline, 2000). Few studies included an inclusion/exclusion criterion to establish the baseline cognitive status of samples, which is problematic because baseline cognitive status may play a substantial role in the response of an individual to CPAP treatment. Additionally, if a sample is not well characterized with respect to baseline cognitive performance, then it becomes difficult for researchers to generalize study results to populations with known levels of cognitive function.

CPAP adherence is another methodological issue present within this literature, as it is well established that many OSAS patients do not correctly follow their prescribed treatment

regimen (Yetkin, 2008). Unfortunately, few studies that used CPAP included a mechanism for tracking adherence in participants, and without this form of monitoring, it becomes impossible to control for the confounding effects of CPAP non-adherence. Studies that contained a tracking mechanism reported that adherence to CPAP treatment was associated with cognitive improvement after three months (Aloia, 2003; Zimmerman, 2006). These findings suggest that adherence is an important factor in predicting the strength of the association between CPAP treatment and cognitive change (Wild, 2004).

A final research consideration in this field is that many neuropsychological tests are susceptible to practice effects. As others have suggested (Aloia, 2003; Ferini-Strambi, 2003; Zimmerman, 2006) alternate forms of the neuropsychological tests should be utilized where possible to minimize the potential for practice effects. However, in the presence of short test-retest intervals, even in within-subjects studies where alternate forms are utilized, practice effects may not be completely diminished.

When this body of work was considered together, no clear trends emerged. Rather, the results of these studies were mixed, and the findings differed greatly in terms of the timing and magnitude of cognitive change that followed CPAP treatment. In fact, several studies have reported that CPAP treatment has no effect on cognitive performance (Engleman, 1998; Monasterio, 2001; Barbé, 2001; Hsu, 2006; Vennelle, 2010). Most other research reported that CPAP had some (at least mild) positive implication for cognitive performance in OSAS patients, especially in the areas of sustained attention (Muñoz, 2000; Lim, 2007; Lau, 2010), psychomotor speed (Ferini-Strambi, 2003; Lau, 2010), and short-term memory (Tonon, 2007). Furthermore, authors suggest that compliant CPAP use is an important factor in determining the magnitude of cognitive improvement (Aloia, 2003; Zimmerman, 2006).

Effect of Pharmacological Intervention on Cognition

Attention is often affected by daytime sleepiness. Because the studies that have investigated cognition following CPAP treatment have produced mixed results, researchers have investigated the possible cognitive benefits of supplemental pharmacological treatment for daytime sleepiness in OSAS. The non-amphetamine stimulant medications modafinil and armodafinil are approved by the United States Food and Drug Administration to treat daytime sleepiness in OSAS patients (Atwood, 2005). In a pilot study of modafinil, long-term memory was improved after two weeks of treatment (Arnulf, 1997). Subsequent RCTs reported that OSAS patients treated with modafinil performed significantly better compared to placebo groups on tests of reaction time (Dinges, 2003) and sustained attention (Dinges, 2003; Bittencourt, 2008) after three weeks (Bittencourt, 2008) and four weeks (Dinges, 2003) of treatment. In RCTs of modafinil effectiveness following acute discontinuation of CPAP treatment, reaction time and sustained attention were better in the treatment group than in the control group in some (Williams, 2010), but not all (Williams, 2008) samples. Differences in episodic long-term memory have been demonstrated within OSAS patient groups treated with CPAP and armodafinil (Hirshkowitz, 2007; Roth, 2008) and in groups treated with only armodafinil (Roth, 2006) compared to control conditions. In general, these findings indicate that stimulant medications might improve memory and attention among adults with OSAS.

Mechanisms Underlying Cognitive Impairment in OSAS

Several mechanisms linking OSAS to cognitive dysfunction have been proposed, and multiple processes likely contribute to this impairment (Figure 1) (Valencia-Flores, 1996; Décary, 2000). In fact, some researchers have argued that the mechanisms underlying the observed cognitive impairment can be distinguished based on the type of cognitive deficit present in OSAS patients (Bédard, 1991; Naismith, 2004).

Daytime somnolence is one proposed cause of cognitive dysfunction in OSAS, particularly in the domains of attention and executive function (Naismith, 2004). In support of this argument, one study reported that slower reaction time was correlated with increased subjective sleepiness in a sample of OSAS patients (Lis, 2008). Work in older adults has suggested that the presence of excessive daytime sleepiness increases the risk for impairment in multiple domains of cognition (Cohen-Zion, 2001; Ohayon, 2002). In the study on the effect of CPAP treatment on cognition in AD, the CPAP treatment also improved daytime sleepiness (Chong et al, 2006), which might have accounted for some of the improvement in overall cognitive function.

A second proposed mechanism for cognitive dysfunction in OSAS is intermittent hypoxemia (Findley, 1986; Greenberg, 1987; Quan, 2011). It has been observed that hypoxemic OSAS patients have worse performance on cognitive tests when compared to non-hypoxemic OSAS patients (Findley, 1986). Elevated measures of hypoxemia in OSAS patients have been associated with declines in motor and processing speed (Quan, 2006; Blackwell, 2011), spatial abilities, processing speed, and mental flexibility (Naismith, 2004), and attention (Shpirer, 2011) in some, but not all (Cohen-Zion, 2004; Lis, 2008) studies. Increased levels of hypoxemia have also been associated with risk of developing dementia or mild cognitive impairment (Yaffe, 2011). This mechanism has been further supported in animal models, where hypoxemia was associated with adverse cognitive outcomes (Row, 2007; McCoy, 2010). Some researchers argue that intermittent hypoxemia, together with sleep fragmentation, leads to prefrontal cortical degeneration, which could explain the impairment in executive function observed in patients with OSAS (Beebe, 2002).

In addition, others have argued that sleep fragmentation is an important mechanistic factor in the development of cognitive impairment in OSAS (Engleman, 1994; Verstraeten, 2004). For example, the number of arousals from sleep is a strong predictor of memory impairment in OSAS (Daurat, 2008). Work in older adults with OSAS has concluded that cognitive decline is related to the number of respiratory disturbances that occurred during sleep – independent of hypoxemia (Cohen-Zion, 2004). In the study on the effect of CPAP treatment on cognition in AD, the CPAP treatment also improved sleep architecture with deeper sleep which might have accounted for some of the improvement in overall cognitive function (Cooke, 2006). In animal studies, sleep fragmentation has been associated with poorer cognitive performance and reduction in neurogenesis (Sportiche, 2010).

Another potential mechanism that may contribute to cognitive impairment in OSAS is disruption in circadian rhythms. Researchers have reported an association between disturbed circadian rhythms (as measured by actigraphy) and severity of cognitive impairment in a sample of nursing home patients (Ancoli-Israel, 1997). A more recent longitudinal study found that older women who had lower amplitude and robustness of activity rhythms, also measured using actigraphy, had significantly greater odds of developing dementia or mild cognitive impairment than older women with the higher amplitude and robustness of activity rhythms (Tranah, 2011). Individuals who repeatedly experience jet lag have been shown to have altered cortisol levels and impaired memory function when compared to control subjects (Cho, 2000). Further, experimental animal research suggests that disruptions of circadian rhythms produce decreases in mental flexibility (Karatsoreos, 2011) and learning and memory (Craig, 2008; Gibson, 2010). Research has also shown that circadian rhythms, as measured through cytokine and hormone levels (Entzian, 1996) and heart rate activity (Noda, 1993), are altered in OSAS patient groups. Although we are unaware of research directly examining circadian rhythms and cognition in samples of OSAS patients, circadian disruptions may contribute to cognitive impairment in this group.

Because the prevalence of OSAS is higher among patients with dementia than among the general population (Ancoli-Israel, 1991; Hoch, 1996; Sharafkhaneh, 2005; Rongve, 2010; Kim, 2011), some researchers have hypothesized that OSAS may contribute to the development of dementia. Further, OSAS and dementia share common risk factors, including the presence of apolipoprotein e4 allele (APOE4) (Bliwise, 2001). This well-known genetic risk factor for Alzheimer's disease and cognitive impairment (Strittmatter, 1993; Caselli, 2004; Crean, 2011) has also been associated with increased risk for OSAS (Kadotani, 2001; Gottlieb, 2004). Some studies have even reported an inverse relationship between AHI severity and global cognitive status (Spira, 2008) as well as memory performance (O'Hara, 2005; Cosentino, 2008) in APOE4 carriers compared to non-carriers. This work suggests that APOE4 status may modify the risk of cognitive impairment in OSAS patients.

A host of other variables may also influence the development of cognitive impairment in OSAS, as many of the most prominent risk factors for OSAS are also risk factors for cognitive impairment. For example, the risk for OSAS increases with age (Young, 1993), as does the risk for cognitive impairment. In one study, younger adults with OSAS performed better on cognitive tests than older adults with OSAS. Although performance did not differ between the younger patient group and age-matched controls, the older patient group showed significant cognitive impairment compared to age-matched controls (Alchanatis, 2008). In addition to being a risk factor for both cognitive impairment and OSAS, increased age represents vulnerability to several other medical conditions and disturbances in sleep duration and architecture (Van Someren, 2000; Ancoli-Israel, 2005). Another primary risk factor for OSAS, obesity, has been associated with cognitive decline (Jeong, 2005) and the development of dementia (Whitmer, 2007; Whitmer, 2008). Cardiovascular illnesses, such as hypertension and stroke, represent other potential mediators in the association between cognitive dysfunction and OSAS, given that studies have identified cardiovascular disease as a risk factor for cognitive impairment (Kilander, 1998) and OSAS (Peker, 2002; Drager, 2010; Pepperell, 2011).

Summary and Conclusion

OSAS is a medical condition of serious clinical and health significance because of its high prevalence, potential for under-diagnosis, and adverse health consequences. Cognitive deficits have long been observed in OSAS patients, and although findings in this domain remain inconsistent, evidence exists for deficits in intellectual function, memory, attention, and executive function in OSAS.

Due to the mixed results of treatment studies, which may be due to variability in inclusion and exclusion criteria, study design, and duration of treatment, it is not possible to make definitive conclusions regarding the impact of CPAP treatment on cognition in OSAS. Although CPAP is a well-established, effective treatment for OSAS, it does not definitively reduce the host of cognitive deficits observed among OSAS patients. In addition to studies of CPAP, we reviewed studies that evaluated the effectiveness of non-amphetamine stimulant medications at improving cognition in OSAS patients. The results from these trials indicate that cognitive performance improved in OSAS patients following treatment with modafinil or armodafinil. Further trials are needed to determine the extent to which stimulant medications, alone or in combination with CPAP, may enhance the daily functioning of patients with OSAS.

Future studies are needed to better understand the mechanisms underlying the causes of cognitive decline in OSAS. This understanding will be achieved through work in neuroimaging and animal models. Large-scale longitudinal RCT studies are needed to

improve our understanding of how cognitive impairment in OSAS patients develops over time. Additional RCTs are needed to determine whether or not CPAP treatment causes cognitive improvement in OSAS patients. Finally, future studies that take a standardized approach to neuropsychological evaluation and subject selection criteria using the diagnostic guidelines set forth by the AASM are needed to aid in comparison of results across studies.

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Figure 1. Potential Contributors to Cognitive Impairment in OSAS

Table 1

RCTs of cognition after CPAP treatment

Author, year	Sample Characteristics	Inclusion Criteria	Study Design	Between-Subject Results	Within-Subject Results
Engleman et al., 1994	N = 32 Age and gender not reported	AHI 5 + 2 symptoms	4 weeks CPAP + 4 weeks oral placebo vs. 4 oral placebo + 4 weeks CPAP	CPAP group better on tests of executive function and attention vs. placebo group	None reported
Engleman et al., 1997	N = 16 Age and gender not reported	AHI = 5.0-14.9 + 2 symptoms	4 weeks CPAP + 4 weeks oral placebo vs. 4 oral placebo + 4 weeks CPAP	CPAP group better on one test of executive function vs. placebo group	None reported
Engleman et al., 1998	N = 23 (91% male) Mean age = 47 ± 12	AHI 15 + 2 symptoms	4 weeks CPAP + 4 weeks oral placebo vs. 4 oral placebo + 4 weeks CPAP	No significant differences	None reported
Engleman et al., 1999	N = 34 (62% male) Mean age = 44 ± 8	AHI = 5.0-14.9 + 2 symptoms	4 weeks CPAP + 4 weeks oral placebo vs. 4 oral placebo + 4 weeks CPAP	CPAP group better on test of attention and executive function vs. CPAP group	None reported
Lojander et al., 1999	N = 27 (all male) Median age = 48	Not reported	CPAP vs. conservative treatment Evaluation baseline vs. 3 months vs. 12 months	CPAP group better on tests of attention vs. CPAP group	None reported
Barbé et al., 2001	N = 54 (91% male) Mean age = 53 ± 2	AHI 30 without daytime sleepiness	CPAP vs. placebo CPAP Evaluation baseline vs. 6 weeks	No significant differences	No significant changes
Bardwell et al., 2001	N = 36 (81% male) Mean age = 47 ± 9	AHI > 15	CPAP vs. placebo Evaluation baseline vs. 1 week	CPAP group better across entire battery of tests vs. placebo group	No significant changes
Henke et al., 2001	N = 45 (56% male) Mean age Group 1 = 50.2 ± 10.4 Group 2 = 50.6 ± 9.7	AHI > 10 with daytime sleepiness or AHI > 20 with or without daytime sleepiness	1 month CPAP vs. 2 weeks placebo CPAP + 2 weeks CPAP Evaluation baseline vs. 2 weeks vs. 1 month	No significant differences	Improvement after CPAP on tests of executive function and sustained attention
Monasterio et al., 2001	N = 125 (86% male) Mean age = 54 ± 9	AHI 10-30 without severe sleepiness	CPAP + conventional treatment (sleep hygiene, weight loss) vs. conventional treatment Evaluation baseline vs. 3 months vs. 6 months	No significant differences	None reported
Barnes et al., 2002	N = 42 (42% male) Middle-aged	AHI = 5-30	8 week CPAP + 8 week placebo pill vs. 8 week placebo pill + 8 week CPAP Evaluation baseline vs. 8 weeks vs. 16 weeks	CPAP group better on tests of executive function vs. placebo group	Improvement after CPAP on tests of verbal fluency and attention
Hsu et al., 2006	N = 30 (66% male) Mean age = 73	AHI 30 stroke patients	8 weeks CPAP vs. 8 weeks conservative treatment Evaluation baseline vs. 8 weeks vs. 6 months	No significant differences	None reported

Author, year	Sample Characteristics	Inclusion Criteria	Study Design	Between-Subject Results	Within-Subject Results
Lim et al., 2007	N = 46 Mean age CPAP = 46.7 ± 2.4 Control = 48.9 ± 3.2	AHI 15	CPAP vs. placebo CPAP + supplemental oxygen vs. placebo CPAP Evaluation baseline vs. 2 weeks	CPAP group better on tests of attention vs. CPAP group	None reported
Ancoli-Israel et al., 2008	N = 52 (75% male) Mean age CPAP = 78.6 ± 6.8 Control = 77.7 ± 7.7	AHI > 10 mild probable AD (MMSE > 17)	6 weeks CPAP vs. 3 weeks placebo CPAP + 3 weeks CPAP Evaluation baseline vs. 3 weeks vs. 6 weeks	No significant differences	Improvement after CPAP on composite test performance after 3 weeks of treatment
Cooke et al., 2009	N = 10 (70% male) Mean age = 75.7 ± 5.9	AHI > 10 mild to moderate AD (MMSE 18)	Nested cross-sectional analysis from RCT Evaluation after 6 weeks of study	CPAP group better on tests of executive function and processing speed vs. group that discontinued CPAP	None reported
Gagnadoux et al., 2009	N = 59 (77% male) Mean age = 50.3 ± 9.1	AHI = 10-60 + 2 symptoms	8 weeks Mad + 8 weeks CPAP vs. 8 weeks CPAP + 8 weeks Mad Evaluation baseline vs. 8 weeks vs. 16 weeks	No significant differences	Improvement after CPAP on two tests of executive function
Vennelle et al., 2010	N = 200 (77% male) Mean age = 50 ± 10	AHI 15 + ESS 10	6 weeks fCPAP + 6 weeks vCPAP vs. 6 weeks vCPAP + 6 weeks fCPAP Evaluation baseline vs. 6 weeks vs. 12 weeks	No significant differences	None reported
Ryan et al., 2011	N = 44 (80% male) Mean age CPAP = 62.8 ± 12.8 Control = 60.7 ± 10.3	AHI 15 Stroke patients	1 month standard rehabilitation vs. 1 month CPAP Evaluation baseline vs. 1 month	No significant differences	Improvement after CPAP on test of attention

Note: AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; fCPAP = fixed-pressure continuous positive airway pressure; Mad = Mandibular Advancement device; MMSE = Mini-Mental Status Examination; vCPAP = variable-pressure continuous positive airway pressure