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Neurocognitive Deficits in Patients with Obstructive Sleep Apnea Syndrome (OSAS)

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1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a common sleep-related breathing disorder affecting 5% of the general population (Young et al., 2002). OSAS is characterized by periodic complete or partial cessation of breathing while sleeping. These recurrent events of breathing result in fragmented sleep and recurrent hypoxemia (reductions in hemoglobin oxygen levels) (American Academy of Sleep Medicine, 1999). It has been documented that OSAS causes excessive daytime sleepiness, mood changes and dysfunctions in several cognitive domains (Engleman & Joffe, 1999; Tsara et al., 2009). However, there are different opinions on which cognitive abilities are affected mostly by OSAS and on the exact nature of cognitive decline. The comparison of the findings of research studies is difficult because of differences in severity of disease, criteria that are used to assess the severity of syndromes and different sample sizes (Quan et al., 2006). Other variables such as the sensitivity of neuropsychological battery chosen (Quan et al., 2006) and different group ages are also confounding factors (Mathieu et al., 2008). Nevertheless, in this chapter an effort is made to review studies which examined neurocognitive deficits in OSAS as well as those which reported the Continuous Positive Pressure Therapy (CPAP) treatment effects on several cognitive domains found to be impaired in OSAS. In addition, the most frequent explanations concerning the mechanism of neurocognitive deficits in OSAS patients and the neuroanatomical pathophysiology of OSAS are discussed.

2. Obstructive sleep apnea – Hypopnea syndrome

Obstructive sleep apnea is part of a spectrum of sleep related breathing disorders which also includes central sleep apnea (CSA) (apnea without respiratory effort, defined as 50% or more of respiratory events are central), mixed sleep apnea (episodes of obstructive sleep apnea and central sleep apnea), upper airway resistance syndrome (increased respiratory effort without apnea or hypopnea) and snoring (Avidan, 2005; Lim et al., 2007). Obstructive sleep apnea/hypopnea syndrome is defined as an obstruction of airflow for 10 seconds or longer. It occurs when the muscles relax during sleep, causing soft tissue in the back of the throat to collapse and block the upper airway. Apnea is characterized by the cessation of airflow (decrements in airflow of $\geq 90\%$) for 10 seconds or more (Avidan, 2005; Lim et al., 2007; Qureshi & Ballard, 2003). On the other hand, hypopnea is usually characterized by a

reduction of $\geq 50\%$ in airflow for 10 seconds associated with a $\geq 4\%$ decrease in oxygen saturation and/or arousal (Tsai et al., 1999) while in accordance with the American Academy of Sleep Medicine guidelines hypopnea is defined as a decrease of $\geq 30\%$ in airflow followed by $\geq 4\%$ oxygen desaturation (Qureshi & Ballard, 2003).

The diagnosis of the syndrome is based on daytime and nocturnal symptoms and especially on a full-night polysomnogram (Andreou et al., 2002), which includes electroencephalographic, electro-oculographic, electromyographic, oxygen saturation, oral and nasal airflow, respiratory effort, electrocardiographic and leg movement recordings (Qureshi & Ballard, 2003). OSAS severity is defined according to apnea-hypopnea index (AHI), by calculating the sum of apneas plus hypopneas per hour of sleep. According to apnea/hypopnea index (AHI), OSAS patients are divided into 3 groups of severity: mild OSAS ($AHI \geq 5$), moderate OSAS ($AHI = 15-30$), and severe OSAS ($AHI \geq 30$) (Qureshi & Ballard, 2003; Tsara et al., 2009). The occurrence of OSAS among children is 1-3 % (Beebe & Gozal, 2002). It affects 2% of women and 4% of men in middle age adults (Young et al., 1993). In older adults (≥ 65 years), it has been reported that 62% of them present hypopnea episodes and 24% have apnea episodes above normative index (Ancoli - Israel et al., 1991). A newest study on a population - based sample of subjects aged 30 to 70 year found that 19% of men and 15% of women have $AHI \geq 10$ (Durán et al., 2001).

Obstructive sleep apnea syndrome is characterized by a perturbation of the pharyngeal dilator muscles associated with or without faulty upper airway anatomy such as macroglossia, hypertrophy of tonsils and long uvula (Avidan, 2005; Qureshi & Ballard, 2003). Other risks factors that enhance the probability of OSAS are obesity, increased neck circumference, positive family history, male postmenopausal status, Down syndrome, Pierre-Robin syndrome, alcohol consumption before bedtime, tobacco and hypnotics use as well as sleeping in supine position (Qureshi & Ballard, 2003; Sánchez et al., 2009). These factors result in episodes of complete or partial upper airway obstruction during sleep and in increased sleep arousals that terminate the apneic episodes. These disturbing events while sleeping cause decreased oxygen saturation as well as sleep fragmentation (Avidan, 2005; Beebe & Gozal, 2002; Qureshi & Ballard, 2003).

In addition, it has been shown that sleep architecture changes in OSAS (Avidan, 2005; Sanchez et al., 2009). A normal sleep cycle consists of a cycling from non-REM sleep (non-rapid eye movement), which consists of four stages (stage 1, stage 2, stage 3, stage 4), into REM sleep (rapid eye movement) with a periodicity that lasts for about 90 min. As the night goes on, stages 3 and 4 become shorter and REM sleep longer. On the other hand, in OSAS, it has been found that stage 2 is increased and stage 1, stage 3, stage 4 and REM sleep decreased (Avidan, 2005; Sánchez et al., 2009), although there are different opinions on the decreased total time of REM sleep (Kiralti et al., 2010; Yaouhi et al., 2009). This abnormal sleep architecture makes sleep lighter and less restorative (Sánchez et al., 2009).

The most well known symptom of obstructive sleep apnea/hypopnea syndrome is excessive daytime sleepiness (Lim et al., 2007; Ferini-Strambi, 2003), although some studies failed to report daytime somnolence (Barbé et al., 2001; Black, 2003). Daytime sleepiness is usually assessed with Epworth Sleepiness Scale (ESS) (Tsara et al., 2009) and the majority of patients with OSAS report that they fall asleep in quiet and monotonous situations such as watching

television, reading a book, or driving a vehicle (Sánchez et al., 2009). Fatigue, non - refreshing sleep, insomnia, loud snoring, gasping, choking, and reports of breathing interruptions by bed partner are common daytime and nocturnal symptoms of sleep apnea (Saunamäki & Jehkonen, 2007). Poor quality of life, poor interpersonal relationships, low work and school efficiency have been observed in OSAS patients (Engleman & Joffe, 1999; Kales et al., 1985). Moreover, patients with OSAS have a high frequency of psychopathology such as depression and hypochondriasis (Kales et al., 1985; Muñoz et al., 2000). In addition, patients with OSAS present increased morbidity due to high rates of cardiovascular diseases and hypertension (Kales et al., 1985; Lattimore et al., 2003) as well as increased mortality (Engleman & Joffe, 1999; Kales et al., 1985).

The treatment of OSAS is based on restoring the upper airway flow. For that reason, the most effective treatment for patients with craniofacial abnormalities is surgical treatment. In the rest of OSAS patients the most effective treatment is the Continuous Positive Pressure Therapy (CPAP) which consists of an air pressure generating device and a fitting mask that is applied over the nose or the mouth of the patient. The positive air pressure maintains upper airway patency and prevents upper airway obstruction while the patients are asleep (Avidan, 2005; Qureshi & Ballard, 2003). CPAP therapy has been shown to improve nocturnal breathing, oxygen saturation (Avidan, 2005), and mean blood pressure (Jaimchariyatam et al., 2010). As a result, it decreases hypertension and the risk of cardiovascular and cerebrovascular events (Lattimore et al., 2003). CPAP therapy also decreases daytime sleepiness (Muñoz et al., 2000) and improves OSAS patients' mood (Engleman et al., 1994) and quality of life (Engleman et al., 1999). However, these positive effects have not been always reported (Barbé et al., 2001).

3. Neurocognitive deficits in obstructive sleep apnea syndrome

Patients with OSAS show deficits across a wide range of cognitive functions including attention, memory, psychomotor speed and visuospatial abilities, constructional abilities, executive functions and language abilities (Andreou & Agapitou, 2007; Engleman & Joffe, 1999; Findley et al., 1986).

3.1 Attention

Patients with obstructive sleep apnea syndrome have been found to show a decline in vigilance (Aloia et al., 2004; Beebe et al., 2003; Décary et al., 2000; Rouleau et al., 2002) and in complex attention (Lau et al., 2010), such as sustained attention (Kotterba et al., 1998), and selective attention (Kotterba et al., 1998). More specifically, research has shown that severe OSAS patients are characterized by diffused impairments in vigilance (Findley et al., 1986; Lim et al., 2007; Muñoz et al., 2000,) and in sustaining attention and alertness (Findley et al., 1986; Lim et al., 2007). It has been shown that a group of OSAS patients of similar severity of disease, displayed poor performance in Stroop Color, TR2 (Reaction Time Test) (Ferini-Strambi et al., 2003), digit symbol and Steer Clear test (Kingshott et al., 2000), tests which assess selective attention, sustained attention and vigilance. The study of Mathieu et al. (2008) is consistent with these results and shows that a group of 28 patients with severe OSAS and mild hypoxemia, compared to 30 controls, gave low scores in sustaining attention and vigilance measured with four-choice reaction time test.

Moderate and severe OSAS patients have been found to show diffused impairment in vigilance assessed with the Steer-Clear test (Engleman et al., 1994). Moreover, a large majority of moderate and severe sleep apnea patients demonstrated attention deficits on vigilance, selective, sustained and divided attention (Mazza et al., 2005). On the other hand, there have been studies on moderate and severe OSAS patients that failed to report deficits in attention measured with digit symbol test (Pierobon et al., 2008), digit span, and letter-sequence subtasks of Wechsler test (Yaouhi et al., 2009).

Moderate OSAS patients performed normally in digit symbol, digit forward subtest of WAIS, Paced Auditory Serial Addition Test (PASAT), and Steer clear tests that assess sustained, divided attention and vigilance (Monasterio et al., 2001). Twigg et al. (2010) did not observe significant attention deficit assessed with Stroop Color test, digit span forward and Trail Making Test A (TMT A) in mild-to-severe OSAS patients. Mild and moderate OSAS patients, compared to a healthy control group, did not present any significant impairments in attention either (Quan et al., 2006). Finally, there has not been observed any poor performance on Steer Clear test and Trail Making test A in patients with mild OSAS (Engleman et al., 1999). In conclusion, there is not any significant attention decline in non-homogenous groups of patients and only severe OSAS patients present poor performance in attention tasks.

3.2 Psychomotor speed

Several studies (Décary et al., 2000; Lau et al., 2010; Rouleau et al., 2002) have noted decrements in psychomotor efficiency, which appeared to be the most consistent explanation for characterizing the profile of neuropsychological test results among OSAS patients. Lim et al. (2007) compared normative data to severe OSAS patients' performance in psychomotor tasks and found a decline in psychomotor speed measured with Digit symbol, Digit vigilance, Trail Making Test A and Stroop color test. However, differences among severe OSAS patients and healthy controls in Trail making test performance have not been always detected (Mathieu et al., 2008). There has been some evidence for psychomotor speed deficit in moderate and severe OSAS patients (Felver - Gant et al., 2007). Yaouhi et al. (2009) also observed a decreased performance in Purdue Pegboard test in a similar group of patients compared to healthy controls. In a recent study, Twigg et al., (2010) did not observe any psychomotor deficits in mild-to-severe OSAS patients measured with TMT. Finally, patients with mild and moderate OSAS compared to controls did not show any significant poor performances on Grooved Pegboard test (GPT), digit symbol or digit search tasks (Quan et al., 2006). Therefore, it is concluded that attention decline prevalence is higher in severe OSAS patients than in moderate or mild OSAS patients.

3.3 Memory and learning

There is a significant number of studies which have shown a serious decline in memory and learning abilities in OSAS patients (Décary et al., 2000), such as episodic memory (Daurat et al., 2008), short-term memory (Borak et al., 1996; Findley et al., 1986; Naëgelé et al., 1998), long-term verbal memory (Aloia et al., 2003) and verbal and visual learning abilities (Feuerstein et al., 1997). In contrast to studies that did not show any immediate memory decline in severe OSAS patients (Grenèche et al., 2011; Mathieu et al., 2008), other studies

found that OSAS patients' performance was poor in short-term verbal memory tests such as digit span test and word list recall (Borak et al., 1996; Lee et al., 2009). The study of Lim et al. (2007) compared normative data to severe OSAS patients' performance on Hopkins Verbal Learning Test (HVLT) and showed a diffused impairment in verbal short and long-term learning and memory. Another study showed that 50% of their OSAS patients presented poor performance in Wechsler memory scale, whereas only 9% of their patients had difficulties in both short and long-term memory (Kales et al., 1985). However, a short-term and long-term verbal memory decline was not always found in severe OSAS patients with an average AHI of 54,95 per hour (Ferini-Strambi et al., 2003). Patients with severe OSAS compared with healthy controls, preserved a good short-term memory and long-term episodic memory measured with digit span forward, immediate recall of Rey Auditory Verbal Learning Test (RAVLT), Digit span backward and delayed recall of RAVLT task. Procedural memory measured with Mirror tracing test was also found intact. Only the performance in immediate recall and the learning of story B of Wechsler memory scale was found decreased (Mathieu et al., 2008).

Regarding working memory, some studies did not find a significant decline in patients with severe OSAS (Ferini-Strambi et al., 2003; Mathieu et al., 2008), whereas other studies did (Grenèche et al., 2011). Severe OSAS patients' also present visual (Borak et al., 1996; Lee et al., 2009; Ferini - Strambi et al., 2003) and spatial memory decline (Borak et al., 1996). Moderate and severe OSAS patients have been presented with poor verbal immediate and delayed recall measured with HVLT (Felver - Gant et al., 2007) RAVLT and Logical Memory Test (Findley et al., 1986; Torreli et al., 2011). However, no significant deficits in episodic memory, measured with verbal logical memory and visual memory of Wechsler test have been observed by Yaouhi et al. (2009). Interestingly, only paired associates - learning curve and percent of retained items in family pictures was impaired (Yaouhi et al., 2009). Pierobon et al. (2008) found significantly lower scores on short-term memory (digit span), and on spatial short-term memory tests (Corsi block test) in their OSAS patients sample in contrast to long-term verbal memory (prose memory test) which was intact. Working memory problems have also been found in moderate and severe OSAS patients assessed with 2-back working memory test, Paced Auditory Serial Addition Test (PASAT) (Felver -Gant et al., 2007) and digit span backward (Torreli et al., 2011). In contrast to this, Yaouhi et al. (2009) did not find any working memory problems in a group of patients of similar severity. No differences between normal and mild-to-severe patients in visual memory and verbal working memory have been found by Twigg et al. (2010). Only immediate and delayed recall of logical memory test as well as spatial working memory were impaired (Twigg et al., 2010). Finally, patients with moderate OSAS did not show any decline in visual or verbal memory assessed with Wechsler Memory Scale (WMS) (Monasterio et al., 2001). Therefore, it seems that memory decline is equivocal in non severe patients and in groups of patients that were not homogenous in OSAS severity.

3.4 Visuospatial and motor constructional abilities

Patients with severe OSAS have been found to have poor visuospatial and constructional abilities measured with tests such as Rey-Osterrieth and Purdue Pegboard (Ferini - Strambi et al., 2003). Aloia et al. (2003) also found poor constructional abilities in severe OSAS patients measured with visual motor integration (VMI) test. Moderate and severe OSAS

patients scored lower on Rey-Osterrieth copy task in comparison to copy drawings and Rey-Osterrieth figure recall (Torelli et al., 2011).

3.5 Executive abilities

The majority of the studies have found executive dysfunctions related to mental flexibility, planning, working memory, analysis, synthesis and organizational skills in OSAS patients (Lau et al., 2010; Saunamäki & Jehkonen, 2007). Low scores in tests such as TMT, block design, Intra-Extra Dimensional Set Shifting test (Meurice et al., 1996; Saunamäki et al., 2009), verbal fluency (Andreou & Agapitou, 2007), digit symbol and copying the Rey - Osterrieth complex figure have been observed in many studies (Feuerstein et al., 1997; Naëgelé et al., 1998). Executive dysfunctions, measured with Raven matrices, Digit symbol, phonemic task of verbal fluency, Letter-number sequencing, Stroop Color-Word test and TMT B, have been observed in patients with severe OSAS (Aloia et al., 2003; Bardwell et al., 2001; Lim et al., 2007; Ferini - Strambi et al., 2003). On the other hand, Mathieu et al. (2008) failed to find several noteworthy low scores in trail making B and Wisconsin test.

Regarding moderate and severe OSAS patients, it has been found that they performed poorly in Trail making test B (Engleman et al., 1994; Felver - Gant et al., 2007) in Stroop test and Digit span (Torelli et al., 2011). On the other hand, there are studies on moderate and severe OSAS patients that did not report any impairment in executive functions assessed with TMT (Pierobon et al., 2008), the phonological task of verbal fluency and Raven matrices (Torelli et al., 2011; Yaouhi et al., 2009).

Mild-to-severe OSAS patients have been documented to have significant impairments in mental shift, planning and working memory measured with Stroop test, Raven matrices, digit span backward and trail making test, and had a minimal decline in phonemic fluency (Twigg et al., 2010). In mild and moderate OSAS patients, Quan et al. (2006) found that executive functions, as measured with Stroop test and Trail making B, were affected a little. In addition, moderate OSAS patients were found to perform among the typical range in digit symbol, block design, PASAT and verbal fluency test (Engleman et al., 1999; Monasterio et al., 2001). Regarding patients' performance on TMT, Monasterio et al. (2001) observed a significant decline in contrast to the findings of Engleman et al. (1999) who did not demonstrate this decline.

It is remarkable that some researchers have found that patients' performance on TMT B (Naëgelé et al., 1998; Ferini - Strambi et al., 2003), Wisconsin card sorting test (Salorio et al., 2002) and letter verbal fluency (Naëgelé et al., 1998; Torelli et al., 2011) are normal although their performance was poor in the rest of neuropsychological tests that are sensitive to the detection of executive dysfunctions. One possible explanation is that there is a pattern of both intact and impaired cognitive functions in OSAS patients that make the executive impairments difficult to detect (Lis et al., 2008). More specifically, Grenèche et al. (2011) proposed that there is a specific working memory deficit associated with complex memory tasks and high level memory scanning. Additionally, it has been suggested that deficits in tasks that require high executive functions are apparent only over the course of the day due to circadian variations or duration of time spent awake (Lis et al., 2008).

3.6 Language functions

Most studies on OSAS patients focus more on cognitive functions such as attention, memory and executive functioning rather than on language abilities. Probably, this is associated with the fact that attention and memory problems are more easily noticed by patients, their bed partners and doctors, than language deficits. It has been reported that 62% of OSAS patients show speech disorders, which correlate with sleep deprivation and its effects on neuromotor function (Monoson & Fox, 1987). Furthermore, there have been reports on OSAS patients that have shown significant semantic language deficits (Andreou & Agapitou, 2007; Feuerstein et al., 1997; Lee et al., 2009), although this has not always been found (Beebe et al., 2003). More specifically, Lim et al. (2007) compared normative data to severe OSAS patients' performance in a verbal fluency test and found a significant impairment in semantic language in 30,4 % of this patient group. Other researchers also noted low scores in verbal fluency tests (Aloia et al., 2003; Bardwell et al. 2001). On the other hand, Ferini - Strambi et al. (2003) have failed to show any significant decline in language abilities concerning semantic verbal fluency in OSAS patients while on the other hand their phonemic verbal fluency was found to be impaired (Ferini - Strambi et al., 2003).

Moderate and severe OSAS patients have been found to show similar performance on semantic word fluency compared to healthy controls (Torelli et al., 2011). Minimal differences between mild -to- severe OSAS patients and healthy volunteers on semantic and phonemic verbal fluency are documented by Twigg et al. (2010). Moderate OSAS patients' verbal fluency was also found to be within normal range by Monasterio et al. (2001). An interesting finding is that mild and moderate OSAS adolescents have shown significantly lower scores on semantic and phonemic tasks of verbal fluency. It is suggested that OSAS occurrence during critical ages of brain growth and development such as childhood and adolescence may cause notable language decline (Andreou & Agapitou, 2007).

4. Neurocognitive improvement on OSAS patients after CPAP treatment

Recent studies have shown that CPAP treatment is related to specific cognitive improvements (Avidan, 2005; Naëgelé et al., 1998). Sánchez et al. (2009), in a clinical review, have concluded that CPAP is effective in reducing symptoms of sleepiness, and improves some cognitive functions. Studying cognitive improvement after CPAP therapy is essential to draw safe results about the permanent cognitive dysfunctions owing to OSAS effects.

4.1 Attention

It has been found that a 1-week CPAP treatment improved attentional ability, although the effect was not significantly beneficial for the patients (Bardwell et al., 2001). Studies that have determined the effects of a 2-week CPAP treatment on severe OSAS patients found a significant improvement in vigilance, alertness and sustained attention (Ferini - Strambi et al., 2003; Lim et al., 2007). Research studies that assessed attention after 4 weeks of CPAP treatment also confirmed this improvement in vigilance and attention (Aloia et al., 2001; Engleman et al., 1994). Engleman et al. (1999) found that a 4-week CPAP treatment had a significant positive impact on attentional abilities measured with PASAT test and digit

symbol test. However, this group of patients with mild OSAS did not show a significant improvement on Steer Clear test. Patients using CPAP for more than 12 weeks showed an even greater improvement in vigilance than patients who were on a 4-week CPAP treatment (Aloia et al., 2001). Another study that evaluated the effects of 3-month CPAP treatment on severe OSAS patients, found an improvement in vigilance and sustained attention performances, assessed with Conner's continuous performance test (Aloia et al., 2003). Studies that evaluated alertness, vigilance and sustained attention after 6 and 12 months CPAP treatment also found a significant decrease in these cognitive dysfunctions (Kingshott, et al., 2000; Kotterba et al., 1998; Muñoz et al., 2000).

On the other hand, Engleman et al. (1998), in a small sample of 23 OSAS patients who were on a 4-week CPAP treatment, did not observe any improvement in attention measured with PASAT test, SteerClear test, TMT and digit symbol test. Barbé et al. (2001) found that a 6-week CPAP treatment in 55 non sleepy patients with severe OSAS did not modify the patients' performance in vigilance and attention, measured with PASAT, TMT and digit symbols. Pelletier-Fleury et al. (2004) also failed to find any significant improvement in attention measured with TMT in patients who were on a 6-month CPAP treatment. However, in this study, OSAS patients were not equaled in terms of age.

4.2 Psychomotor speed

Bardwell et al. (2001) showed that a 1-week CPAP treatment did not improve very severe OSAS patients' performance in Stroop Test and TMT. On the other hand, Lim et al. (2007) have shown that a 2-week CPAP treatment can significantly decrease the time to complete tests that measure psychomotor speed, such as digit vigilance, Stroop test and Trail Making Test A in severe OSAS patients. Studies on the effects of 3- and 6-month CPAP therapy on cognitive functions of severe OSAS patients observed a decrease in motor speed functions assessed with Purdue Pegboard test (Aloia et al., 2003) and in reaction time measured with TMT, PASAT test (Hoy et al., 1999) and digit symbol test (Kingshott et al., 2000). However, psychomotor speed improvement was not always found in moderate and severe OSAS patients (Felver - Gant et al., 2007) and non sleepy patients (Barbé et al., 2001). In another study, Engleman et al. (1998) did not find psychomotor speed improvement on severe OSAS patients after 4 weeks CPAP treatment. Finally, another study assessing the long-term effects of CPAP, (Muñoz et al., 2000) found that a 1-year CPAP therapy changed only a little OSAS patients' reaction time measured with Psychometer vigilance test.

4.3 Memory and learning

Short-term CPAP treatment for 1 or 2 weeks did not notably improve severe OSAS patients' short- after and long-term verbal memory, visuospatial and working memory, as well as learning ability measured with Hopkins verbal learning test, digit span and Brief visuospatial memory test (Bardwell et al., 2001; Lim et al., 2007). On the other hand, Ferini - Strambi et al. (2003), found that 2-weeks and 4-months CPAP therapy had a significant positive impact on visuospatial learning tasks on 23 severe OSAS patients. According to other studies, a 3-month CPAP treatment had a positive effect on non-verbal recall task (Aloia et al., 2003) and working memory task (Felver - Gant et al., 2007). Borak et al. (1996) found that 20 severe OSAS patients who were on a 3-month CPAP treatment had a

significant improvement in recent verbal, visual and spatial memory. In addition, an over 12-month CPAP therapy resulted in considerable improvement on verbal, visual and spatial memory in severe OSAS patients (Borak et al., 1996).

On the other hand, a 1.5-months of CPAP treatment did not modify memory functions of non-sleepy patients with severe OSAS (Barbé et al., 2001). Short-term memory impairment was also persistent in OSAS patients despite 4 and 6 months CPAP treatment (Feuerstein et al., 1997; Naëgelé et al., 1998) in contrast to learning disabilities and long-term memory decline (Feuerstein et al., 1997) which improved.

4.4 Visuospatial and motor constructional abilities

It has been observed that severe OSAS patients' performance in assembly trail of Purdue Pegboard test improved significantly after 2-weeks (Ferini - Strambi et al., 2003), 3-months (Aloia et al., 2003) and 4-months CPAP treatment (Ferini - Strambi et al., 2003). However, no significant improvement in tasks that require high mental processes such as visual motor integration (VMI) was observed (Aloia et al., 2003). No significant improvement has been found in Rey - Osterrieth complex figure after 4-months (Ferini - Strambi et al., 2003) and 6 months CPAP therapy (Saunamäki et al., 2009). The above findings led Aloia et al. (2004) to conclude that CPAP treatment failed to improve patients' performance in constructional tasks.

4.5 Executive abilities

Short-term CPAP treatment for 1 and 2 weeks did not improve significantly patients' performance in Stroop Color - Word test, TMT B and Letter - number sequencing (Bardwell et al., 2001; Lim et al., 2007). However, 3-week and 4-week CPAP treatment has been shown to improve mental flexibility measured with TMT (Engleman et al., 1994; Meurice et al., 1996). Engleman et al. (1999) observed that patients' performance in digit symbol and PASAT test was improved, in contrast to TMT and blocks design performance (Engleman et al., 1999). Longer CPAP therapy (3-months) has been found to reverse the impairment in executive functions, since patients improved their performance in Verbal fluency test - Phonemic task and Trail making test B (Aloia et al., 2003), in contrast to another research study which did not find this improvement (Felder-Gant et al., 2007). Longer CPAP treatment for 4 or 6 months has also been found to improve executive functions, such as planning capacities and working memory (Feuerstein et al., 1997; Naëgelé et al., 1998; Saunamäki et al., 2009). Yet, patients with 6 months CPAP treatment did not completely reverse executive dysfunctions measured using Rey - Osterrieth complex figure test (Saunamäki et al., 2009). It seems that high order executive functions or specific domains of executive functions do not improve after CPAP treatment.

4.6 Language functions

There are a few research studies that explored the effects of CPAP treatment on language functions. 1- to 2-week treatment with CPAP failed to improve significantly patients' performance in verbal fluency tasks (Bardwell et al., 2001; Lim et al., 2007) and in Boston naming test (Aloia et al., 2003). A study on severe OSAS patients found that their semantic

verbal fluency performance improved after a 15-day CPAP treatment although there was not a statistically significant difference between the healthy subjects' performance and that of OSAS patients before the treatment (Ferini - Strambi et al., 2003).

In conclusion, cognitive deficits in OSAS patients are partially reversible if treated with CPAP. More specifically, CPAP seems to improve only some aspects of cognitive functions. Neurocognitive deficits in high executive functions and verbal fluency do not seem to improve after CPAP treatment (Ferini - Strambi et al., 2003; Montplaisir et al., 1992). It is possible that hypoxemia may have caused permanent brain injury. On the other hand, cognitive tasks such as attention, psychomotor speed and memory that require low mental activation seem to improve after CPAP treatment. It is suggested that the improvement of these cognitive functions are due to improvement of daytime sleepiness and quality of sleep. The diversity in research results reflects differences in methodology, treatment duration, low tolerance of treatment, severity of OSAS, insufficiently sensitive neuropsychological measures and variability of the sample (Sánchez et al., 2009).

5. Mechanism of cognitive impairment in OSAS patients

The cause of cognitive deficits in OSAS patients is complicated. Some researchers have shown a significant correlation between cognitive impairment and daytime sleepiness related to sleep fragmentation resulting from frequent apneas (Valencia-Flores et al., 1996; Verstraeten, 2007) while others attribute cognitive decline to nocturnal hypoxemia (Berry et al., 1986; Findley et al., 1986). Finally, some researchers attribute cognitive impairments to a combination of PSG parameters (AHI, sleep arousals, oxygen desaturation, sleep architecture) (Cheshire et al., 1992; Quan et al., 2006).

More specifically, Verstraeten et al. (2004) proposed that low order deficits such as attentional decline and slow mental processing underlie the more complex deficits found in executive functions. In this study, attention, vigilance and executive functions were assessed with TMT A, B, Stroop color -Word test and Symbol digit Modalities. The cognitive decline was comparable to the decline found after sleep loss. It has been concluded that sleep disruption has a pervasive influence on cognitive functions and affects not only underlying lower level processes such as arousal and alertness, but also higher - level cognitive processes such as executive functioning. In other words, high order cognitive dysfunction can be explained by impairment in both attentional decline and psychomotor speed decrements due to sleepiness (Verstraeten & Raymond, 2004). However, a discussion of sleep fragmentation and hypoxemia is limited in this model.

Another explanation for the cognitive deficits found in OSAS patients suggested that attentional deficits and memory impairments are affected by sleep fragmentation while impairments in executive functions, in constructional abilities, in motor tasks and in language are caused by hypoxemia (Bérard et al., 1991; Kotterba et al., 1998; Naëgelé et al., 1995). More specifically, attention decline was linked to vigilance impairment that derives from changes in sleep architecture (Bédard et al., 1991; Montplaisir et al., 1992). Ferini-Strambi et al. (2003) also found that sustained attention was correlated with daytime sleepiness. Regarding the relation between psychomotor speed and hypoxemia, a significant interrelation was found (Bédard et al., 1991; Findley et al., 1986; Kotterba et al., 1998; Grenèche et al., 2011). Quan et al. (2006) observed this interrelation in mild and moderate

OSAS patients. More severe oxygen desaturation was associated with poorer motor performance and lower processing speed whereas stage 1 sleep, sleep arousals and daytime sleepiness were not correlated with these deficits (Quan et al., 2006). Regarding memory dysfunctions, it has been found that vigilance impairment due to sleep changes contribute to memory decline (Bérard et al., 1991; Montplaisir et al., 1992). Recently, studies on sleep architecture (percentage of slow wave sleep and rapid eye movements sleep) have shown that sleep architecture is negatively associated with immediate memory (forward digit span) and low level memory scanning (simple Sternberg) (Grenéche et al., 2011). In addition, Daurat et al. (2008) showed that the best predictor of episodic memory deficit was the number of microarousals. Constructional abilities have been found to positively associate with the time that oxygen saturation levels are below 80% (Aloia et al., 2003). Executive dysfunctions and hypoxemia seem to be interrelated (Findley et al., 1986; Montplaisir et al., 1992). Ferini-Strambi et al. (2003) showed a significant correlation between the time of oxygen saturation (SaO₂) below 90% or lowest peaks of SaO₂ and the phonemic fluency or the Rey figure in severe OSAS patients. It has been reported that working memory and high-speed memory scanning deficits, factors pertaining to executive functions, are associated with the degree of hypoxemia (mean SaO₂) (Aloia et al., 2003; Grenéche et al., 2011). Regarding verbal disabilities, it has been found that hypoxia could predict patients' performance on verbal fluency test (Berry et al., 1986).

However, this explanation of cognitive deficits needs further elucidation as there are studies that failed to associate memory functions with sleep arousals, sleep architecture (Findley et al., 1986), daytime sleepiness (Lojander et al., 1999) or severity of disease (Lojander et al., 1999; Twigg et al., 2010). Some other studies found a link between hypoxia and attention (Kotterba et al., 1998), verbal and non-verbal memory (Berry et al., 1986; Findley et al., 1986) as well as delayed recall (Aloia et al., 2003). On the other hand, the total time of SWS and REM amount were associated with language and executive functions respectively (Lee et al., 2009). Moreover, there is a research study which failed to associate executive functions, such as working memory, with hypoxia (Felver-Gant et al., 2007). Some other studies found that a specific cognitive decline such as verbal delayed memory impairment is associated with both sleep fragmentation and oxygen desaturation (Aloia et al., 2003; Kiralti et al., 2010).

Beebe and Gozal (2002) have suggested that the frontal lobes of the brain are affected by sleep fragmentation and hypoxemia. Sleep fragmentation is proposed to affect frontal lobes by disrupting the normal restorative processes of sleep, while hypoxemia causes cellular changes in the prefrontal cortex. A recent study on a small group of severe OSAS patients suggested that both hypoxia and sleep fragmentation contribute to frontal dysfunction (Xi et al., 2011). However, this explanation model of cognitive deficits includes exclusion of brain regions other than frontal lobe and little discussion of the nuances of executive functions. Moreover, there are studies that do not ascribe cognitive dysfunctions to both hypoxia and sleep deprivation, i.e., in tasks that assess verbal short-term and long-term memory, non verbal memory, constructional abilities, language (Mathieu et al., 2008; Pierobon et al., 2008; Torelli et al., 2011), attention and executive functions (Lis et al., 2008; Mathieu et al., 2008; Mazza et al., 2005).

Another model, the microvascular theory, has been proposed by Aloia et al (2004). This model suggests that a vascular compromise might exist in the small vessels of the brain and the intermittent hypoxemia of OSAS may affect the regions of the brain that are

metabolically active during hypoxemia. Microvascular disease of small vessels that feed white matter of the brain may result in deficits of attention, mental processing, memory executive functions, motor speed and coordination. Recent studies have shown that hypercapnia, cortical and sympathetic activation in OSAS patients cause cardiovascular, cerebrovascular and metabolic disease as well as sudden death (Lloberes et al., 2011). More specifically, repetitive episodes of deoxygenation and reoxygenation increase the production of proinflammatory cytokines (TNF), C-reactive protein and chemoreceptors that are associated with the development of atherosclerosis and high arterial pressure (Lloberes et al., 2011). However, hypoxia, hypercapnia, sleep fragmentation, hemoglobin levels, inflammation parameters and comorbidities are unlikely to account for all cognitive dysfunctions (Dodd et al., 2010).

Beebe (2005) proposed that multiple factors affect the neurocognitive functions in OSAS. It has been suggested that sleep fragmentation and hypoxemia effects are intermingled and synergistic. He proposed that these synergistic mechanisms interact with vulnerable brain regions such as hippocampus, prefrontal cortex, subcortical gray and white matter, suggesting the potential involvement of small vessels in the brain. Regarding the complexity of higher order cognitive abilities such as executive functions, Beebe (2005) suggested that these higher order functions may be dependent on task demands, or the environment of testing, while some specific deficits may be related to some tasks but not others. Other factors such as sociodemographic factors, previous experience on testing and genetic endowment, may also affect cognitive performance (Beebe, 2005). Moreover, Mathieu et al. (2008) found that younger OSAS patients are more sensitive than older OSAS patients to sleep defragmentation and hypoxia. Another study found that socioeconomic status and adolescent cognitive ability may explain verbal disability, verbal memory decline, or rate of impairment in memory (Richards et al., 2005). Finally, Alchanatis et al. (2005) have proposed that intelligence and cognitive functions are interrelated. In other words, high - intelligence may have a protective effect against cognitive decline in OSAS patients, due to increased cognitive reserve.

6. Neuroanatomical pathophysiology of OSAS

In obstructive sleep apnea syndrome, compared to other sleep disorders, at least two primary nocturnal abnormalities occur: hypoxemia and sleep fragmentation. It has been found that a decreased oxygen transport to brain cells modifies ion channels (potassium, sodium, calcium) and as a result cell excitability increases. In addition, it causes alterations in neurotransmitters (dopamine, acetylcholine, ATP), and reduces respiration followed by enhancement of sympathetic and respiratory activities which result in changes involving modification in signaling pathways, in neuromodulators and their receptors as well as genome effects (Areza-Fegyveres et al., 2010; Powell, 2007). It has also been found that frequent oxygen desaturation during everyday activity elevates choline level in frontal brain areas and high levels of choline damage myelin and membrane precursors (Gibson et al., 1981). Hypoxia is also associated with enhancement of hemoglobin concentration level, which can affect cognitive abilities (Grant et al., 1982). Moreover, it may increase hematocrit level and angiogenesis through enhancement of production of vascular growth factors (Areza-Fegyveres et al., 2010). Finally, it is believed that hypoxia, inflammation and oxidative stress initiate the process of endothelial dysfunction that plays a significant role in

vascular tone and cellular growth (Butt et al., 2010). Some regions of the brain, such as the hippocampus, basal ganglia, cerebellum, occipital cortex and frontal regions are more susceptible to oxygen deprivation than others (Martin et al., 2011). More specifically, functional magnetic resonance image (fMRI) studies revealed a significant gray matter loss and atrophy in several brain regions including cortex, hippocampus and striatum suggesting that chronic exposure to hypoxia results in neuronal damage and impaired cognitive functions (Maiti et al., 2008; Shukitt-Hale et al., 1996).

Regarding sleep loss effects on brain, it has been found that it decreases pineal melatonin production which causes disturbances in circadian physiology of cells, organs, neurochemicals, neuroprotective and other metabolic functions (Jan et al., 2010). Moreover, it has been found that short-term and long-term sleep deprivation has both been associated with the upregulation of hundreds of genes in the cerebral cortex and other brain areas. This includes genes that are associated with energy metabolism, memory formation, memory consolidation, protein synthesis and synaptic depression (Cirelli et al., 2006). It is well established that chronic sleep deprivation or sleep fragmentation in healthy subjects may cause decline in alertness, simple attention, psychomotor speed as well as learning, memory, working memory and executive functions (Killgore, 2010; Whitney & Hinson, 2010; Reynolds & Banks, 2010). A functional magnetic resonance imaging (fMRI) study has shown the negative impact of sleep deprivation on specific brain regions, such as temporal to parietal regions and frontal lobe regions (Jan et al., 2010). In addition, it has been suggested that long-term sleep deprivation may cause permanent neuronal alterations especially in memory related brain regions, such as hippocampus (Jan et al., 2010). Killgore (2010) observed that chronic sleep deprivation is followed by reduced activation of frontal and parietal networks and alters functioning within the thalamus.

Regarding the neuropathophysiology of OSAS, patients are presented with blood flow reduction during apneic episodes in left frontal and temporal lobes (Kıraltı et al., 2010). Yaouhi et al. (2009) found a right-lateralized decreased brain metabolism in precuneus, middle and posterior cingulate gyrus, and the parieto - occipital cortex, as well as the prefrontal cortex (Yaouhi et al., 2009). Joo et al. (2007) also found reduced cerebral blood flow during wakefulness in bilateral hippocampal gyri, right lingual gyrus, precentral gyrus, and cuneus in patients with severe OSAS. These findings may partly explain the deficit in memory, spatial learning, executive function, and attention which are frequently found in OSAS patients (Joo et al., 2007). Xi et al. (2011), using fMRI, observed that OSAS patients showed a decreased mismatch-related activation in frontal regions such as prefrontal cortex and anterior cingulate, whereas an increased activation was only found in the right anterior prefrontal gyrus. Another study (Joo et al., 2009) which used fMRI to assess gray matter volume in OSAS patients, has found reduced brain gray matter concentration in left gyrus rectus, bilateral superior frontal gyri, left precentral gyrus, bilateral frontomarginal gyri, bilateral anterior cingulate gyri, right insular gyrus, bilateral caudate nuclei, bilateral thalami, bilateral amygdala hippocampi, bilateral inferior temporal gyri and bilateral quadrangular and biventer lobules in cerebellum. These results suggest that memory impairment, executive dysfunctions, cardiovascular disturbances, and dysregulation of autonomic and respiratory control might be related to morphological differences in the brain gray matter areas (Joo et al., 2009). Yaouhi et al. (2009) observed gray matter loss in frontal and temporo-parietal-occipital cortices, the thalamus, hippocampal

region, some basal ganglia and cerebellar regions mainly in the right hemisphere. Brain morphological changes have also been found in moderate and severe OSAS patients. Volumes of cortical gray matter, such as right and left hippocampus and more lateral temporal areas were also found to be smaller in severe OSAS patients compared to controls (Torelli et al., 2011).

As we have seen, hypoxia and sleep fragmentation cause cellular and molecular changes that lead to disruption of functional homeostasis and altered neuronal and glial viability within particular brain regions (Beebe & Gozal, 2002; Morrell et al., 2003), such as frontal lobe (Beebe et al., 2002; Fuster, 2000; Koechlin et al., 1999) and temporal cortex (Yaouhi et al., 2009). Moreover, hypoxia and sleep deprivation modulate the expression of inflammatory mediators such as interleukins and tumor necrosis factor alpha (Butt et al., 2010). In summary, the pathophysiology of cognitive deficits in OSAS patients is multifactorial. Since OSAS affect multiple brain regions, brain damages may result from several etiologies such as hypoxemia, sleep deprivation, small vessel damages, chronic inflammation, all of which can result in local ischemic episodes (Matthews & Aloia, 2011).

7. Conclusions

In this thorough review of literature, we have shown that the majority of OSAS patients suffer from attentional, memory and psychomotor speed decline, while others present impairments in high order cognitive functions such as executive and language functions. CPAP treatment is not always helpful in improving cognitive functions, suggesting that OSAS may cause permanent damages in specific brain regions. The effects of sleep fragmentation, hypoxemia, low CBF, inflammation parameters and vasocerebral diseases on cognitive functions are intermingled and synergistic. However, these conclusions need to be treated with caution since most studies are not homogeneous in OSAS severity. Moreover, the diversity in the findings of the research studies presented may be due to differences in methodology and in the types of neuropsychological tests which were used to assess cognitive functions. Furthermore, the treatment duration, low tolerance of treatment, and disease duration are not often taken into account in most studies. Therefore, more research is needed to elucidate the etiology of OSAS and investigate further to what extent sleep architecture, cerebral blood flow, gas blood, inflammation parameters, co-morbidities or even socioeconomic factors have a negative impact on cognitive functions in OSAS patients.

8. References

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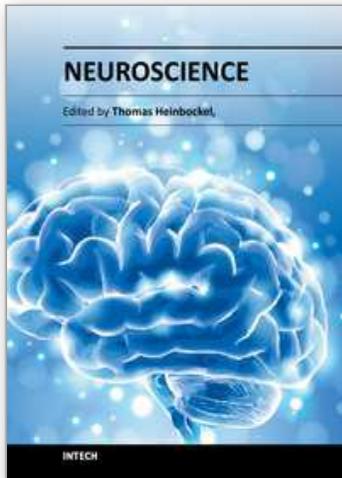
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