Sleep apnea syndrome and cognition

Health & Medicine

Introduction

Previous studies investigating the effects of obstructive sleep apnea (OSA) on alertness and cognitive functions have demonstrated that apnea recurrence, sleep fragmentation, and nocturnal hypoxemia may affect diurnal behavior, cognitive function, and well-being in these patients. A wide range of cognitive impairment has been identified in OSA patients, from attention and vigilance to memory and executive functions (Jackson et al., 2011). A still controversial point is which factor is mainly responsible for the cognitive impairment, given that up to now all considered factors, i. e., sleep fragmentation, sleepiness, apnea + hypopnea index (AHI), and hypoxemia, showed weak correlation with cognitive scores. Moreover, standard measures used in the clinical setting do not provide a reliable assessment of cognitive dysfunction, particularly in elderly subjects in whom it is difficult to differentiate between the age-related cognitive decline and the OSA-related impairment.

In this review, current knowledge about the type of cognitive dysfunction and the mechanisms underlying cognitive impairment are reviewed. Then we summarize what is know about cognitive dysfunction in the elderly in whom conflicting results are reported in the literature. These controversial data open discussion on the effect of therapy on cognitive dysfunction.

Incidence of Sleep Apnea Syndrome

Previous studies on sleep-related breathing disorders have focused on OSA to indicate a clinical entity characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, inducing falls in oxygen

saturation, and hypercapnia. To restore pharyngeal patency, patients have recurrent arousals from sleep, inducing sleep fragmentation and sleep discontinuity. The nocturnal hypoxemia and the recurrent arousals contribute to the development of sleepiness, hypertension, and cognitive impairment. Several factors increase the OSA risk such as genetic predisposition, obesity, upper airways shape (Pillar et al., 2000), craniofacial morphology (Schellenberg et al., 2000), hormonal influences (Bixler et al., 2001), and APOE4 phenotype. (Gottlieb et al., 2004)

Prevalence studies conducted over the past decades (Young et al., 1993 ; Quan et al., 1997 ; Bixler et al., 2001) have demonstrated that up to 5% of adults in Western countries are likely to have undiagnosed OSA. When we consider the severity of the disease stratified according to an AHI ≥ 5 and an AHI ≥ 15, the prevalence is from 3 to 28% for mildly severe cases (AHI > 5) and from 1 to 14% for moderately severe cases (AHI > 15). Results of cohorts in Wisconsin (1490 subjects; Young et al., 1993), Pennsylvania (932 subjects; Bixler et al., 1998 , 2001), Spain (455 subjects; Duran et al., 2001), and from the Sleep Heart Health Study (6642 subjects; Quan et al., 1997) have demonstrated that 1 in every five adults has at least an AHI > 5 and 1 in every 15 has at least an AHI > 15. In community-dwelling older adults (age 65–95 years), 81% of participants had an AHI > 5, with prevalence rates of 62% for an AHI > 10, 44% for an AHI > 20, and 24% for an AHI > 40 (Ancoli-Israel et al., 1991). Furthermore, in about 6000 older adults aged 63. 5 years examined in the Sleep Heart Health study (Young et al., 2002) the authors found that in subjects aged 60–69 years, 32% had an AHI between 5 and 14, and 19% an AHI > 15. The rising trend in elderly subjects may be

explained by changes in the anatomy or function of the upper airway (Eikermann et al., 2007) or by the coexistence of other medical disorders, i. e., diabetes, hypertension, and cardiovascular disease. However, recent data suggest that in the elderly, the cut-off point of an AHI of 5 or 10 (Ancoli-Israel and Coy, 1994) is a less sensitive marker in distinguishing subjects with or without OSA, an AHI ≤ 15 being present in the majority of healthy elderly subjects (Pavlova et al., 2008). This would support the hypothesis (Bliwise, 1994 ; Bixler et al., 1998 ; Pavlova et al., 2008 ; Lavie and Lavie, 2009) that the presence of a greater AHI in the older population may reflect either an age-related or an age-dependent disease, the first inducing the typical OSA symptoms, and the second having fewer clinical consequences.

Cognitive Performance and OSA

Despite differences in the definition of OSA syndrome, several studies suggest that apnea recurrence, sleep fragmentation, daytime sleepiness, and nocturnal hypoxemia may induce an impaired cognitive function in OSA patients (Kim et al., 1997 ; Engleman and Joffe, 1999 ; Engleman et al., 2000 ; Adams et al., 2001) affecting attention, vigilance, memory, psychomotor performance, and executive function (Beebe et al., 2003 ; Aloia et al., 2004 ; Jackson et al., 2011). However, the presence and the extent of the cognitive changes in OSA subjects is still a matter of debate, the cognitive impairment worsening with disease severity but not linearly (Bedard et al., 1991 ; Boland et al., 2002). One study stresses that although sleepiness and hypoxemia might cause the neuropsychological deficits in OSA patients, the co-morbidities usually observed in these patients, i. e., cardiovascular diseases, obesity, physical inactivity, are more important than sleep apnea

per se in affecting neurocognitive functions (Lim and Veasey, 2010). Finally, we have to consider that there is a large heterogeneity in the neuropsychological tests used in OSA patients making it difficult to compare the results (Décary et al., 2000).

Bearing in mind these limitations, in recent years special interest has focused on impairments of executive function that refer to the ability to develop and sustain an organized goal-directed and flexible approach to problem situations and to allow individuals to use adaptively their basic skills in a complex and changing external environment. This domain could be examined by tests demanding working memory, mental flexibility, planning, organization, and problem solving (Fulda and Schulz, 2001 ; Saunamaki and Jehkonen, 2007), tasks related to prefrontal cortex activity (Beebe and Gozal, 2002). Results of studies on cognitive function in OSA are heterogeneous, some studies suggesting an executive dysfunction (Bedard et al., 1991 ; Naëgele et al., 1995 ; Boland et al., 2002 ; Ferini-Strambi et al., 2003 ; Lis et al., 2008 ; Torelli et al., 2011), and others an attentional impairment (Redline et al., 1997 ; Lee et al., 1999 ; Salorio et al., 2002 ; Verstraeten and Cludydts, 2004 ; Gosselin et al., 2006 ; Yaouhi et al., 2009 ; Quan et al., 2011). The controversial results may be partially explained by the severity of the disease, a minor cognitive impairment present in mild cases (Redline et al., 1997 ; Gosselin et al., 2006 ; Lis et al., 2008) and a greater deficit particularly in terms of executive function (Naëgele et al., 1995 ; Ferini-Strambi et al., 2003 ; Aloia et al., 2004) in severe cases (AHI circa 50).

In some studies supporting an executive dysfunction, performance deficits are not only reported in executive tests but in all examined cognitive abilities, (Naëgele et al., 1995 ; Feuerstein et al., 1997 ; Boland et al., 2002) suggesting a global cognitive impairment. As suggested by Verstraeten and Cludydts (2004) , a methodological bias in the assessment of executive function is the lack of control of attention performances during the task, OSA patients showing a decline in the ability to sustain attention (Dinges and Kribbs, 1991) and having alertness instability (Doran et al., 2001). These two factors influence their performance. To overcome this limitation, two studies (Naëgelé et al., 2006 ; Lis et al., 2008) performed a combined evaluation of the executive function and alertness, measuring both n-back task and reaction time performances. Naëgelé et al. (2006) found that the untreated OSA group did not differ from the control group on dual tasks, e. g., combined auditory and visual digit span, that measure attentional resources. In contrast, they differ in the maintenance and processing components of working memory, suggesting that OSA subjects have difficulties in the processing of new information without attention deficit. In contrast, Lis and coworkers (Lis et al., 2008) performing a combined evaluation of executive function (i. e., repeated working memory), and alertness (i. e., repeated reaction time and subjective and objective sleepiness assessment), found a decline in reaction time on all tasks and a lowered accuracy only in the n-back test, suggesting a deficit in attention and more basic cognitive processes.

In terms of memory, studies in middle-aged patients (Salorio et al., 2002 ; Naëgelé et al., 2006 ; Yaouhi et al., 2009) found a minor impairment in word

list learning and slightly decreased recall in a visual episodic memory task. Naëgelé et al. (2006) observed a free recall deficit in episodic memory but normal maintenance and recognition, confirming that the memory impairment in OSA is mild (Fulda and Schulz, 2001) and does not affect all memory processes (Naëgele et al., 1995 ; Salorio et al., 2002 ; Naëgelé et al., 2006).

Effects of Treatment

The current treatment of choice in OSA patients is the continuous positive airway pressure (CPAP) inducing a significant improvement in daytime sleepiness (Engleman et al., 1996), a reduction in occupational, work, and road accidents (Cassel et al., 1996) as well as an improvement in general health (Reimer and Flemons, 1999 ; Sanner et al., 2000 ; Barbé et al., 2001 ; McFadyen et al., 2001). When we consider the effect of CPAP on the cognitive function, we can see that while some deficits can be improved by therapy, other domains such as executive function remain unchanged (Matthews and Aloia, 2011). To exclude the effect of an insufficient treatment, Weaver et al. (2007) examined patients before and after CPAP therapy considering the objective adherence to treatment. They found that, even among patients using CPAP for more than 7 h per night, only 30% of these patients had a normalization of objective sleepiness and only 50% had normal results on the Functional Outcome of Sleep questionnaire. Zimmermann et al. (1996) studied verbal memory changes in 58 memory-impaired OSA patients after 3 months of CPAP therapy. They found a dose-response relationship between the level of CPAP adherence and the extent of improvement in verbal memory with, however, a third of the patients with 6

h adherence not showing any improvement. Similar data were reported by Antic et al. (2011) and Lau et al. (2010) confirming that even the most optimally treated OSA patients may not experience a complete reversal in attention and executive function, probably due to a permanent brain alteration in severe cases (Bedard et al., 1993 ; Naëgele et al., 1995 ; Feuerstein et al., 1997 ; Ferini-Strambi et al., 2003).

Pathogenesis of Cognitive Impairment

In large epidemiological studies (Kim et al., 1997 ; Boland et al., 2002) analyzing memory and cognitive and psychomotor functions, some authors found that OSA severity, as indicated by the AHI, was significantly related to diminished psychomotor efficiency with, however, a weak correlation. Similar findings were described in the Danish MONICA study cohort comprising of 848 participants (Jennum and Sjol, 1994) in that an AHI > 5 was associated with self-assessed concentration problems but not with memory impairment. Today there is general agreement that not apnea recurrence in itself, but the associated sleep fragmentation and nocturnal hypoxemia, are the key factors affecting cognitive function in patients with OSA (Bedard et al., 1991 ; Redline et al., 1997 ; Engleman and Joffe, 1999 ; Daurat et al., 2008). This hypothesis has been confirmed by animal studies showing that both intermittent hypoxia (Kalaria et al., 2004 ; Xu et al., 2004) and sleep fragmentation (Tung et al., 2005 ; Nair et al., 2011), two essential features of the OSA syndrome, can independently lead to neuronal loss in the hippocampus and prefrontal cortex, areas closely associated with memory processes and executive functions.

According to Beebe and Gozal (2002) , the prefrontal cortex is selectively susceptible to both sleep deprivation and hypoxemia. The prefrontal cortex may exert modulatory influences on lower-level processes sub-served by posterior cortical regions (Knight et al., 1999) that have biological vulnerability to sleep loss and sleep fragmentation (Horne, 1993 , 1998 ; Thomas et al., 2000). Moreover, attention control is believed to rely on the prefrontal cortex and its interaction with the thalamus that we know is implicated in alertness, vigilance and selective and sustained attention (Portas et al., 1998 ; Jones and Harrison, 2001). If so, a combined deficit in executive and attention skills is to be expected in OSA patients. It might be suggested that at the beginning of the disease when patients are asymptomatic or showing minimal cognitive impairment, a chemical and dysfunctional brain injury could occur, reflected in increased compensatory frontal activation during executive tasks. During the progression of the disease, the chronic recurrence of apneas and the progressive worsening of the hypoxemic stimulus will induce structural brain lesions, explaining the greater cognitive alteration, the impairment of executive tasks, and the lack of cognitive normalization after treatment.

Role of Sleepiness and Sleep Fragmentation

Experimental reports (Dinges and Kribbs, 1991 ; Dinges et al., 1997 ; McCoy and Strecher, 2011) in healthy subjects assumed that cognition varies in parallel with changes in alertness, supporting the hypothesis that sleepiness is the major factor underlying performance impairment. However, when we consider OSA patients, there is no linear relationship between the degree of sleepiness and cognitive impairment, suggesting that in these patients

cognitive impairment is related more to an instability state (Doran et al., 2001) acting on vigilance and attention than on executive dysfunction (Verstraeten and Cludydts, 2004). Moreover, OSA patients without notable cognitive impairment have been found in approximately half of a non-clinical population (Quan et al., 2006) as well as in an elderly community population (Bixler et al., 1998 ; Sforza et al., 2010), suggesting that there are some factors protecting OSA patients from substantial cognitive deficits (Beebe et al., 2003). These factors include sleep deprivation tolerance (Mu et al., 2005) and cognitive reserve that allow sleep-deprived subjects (Drummond et al., 2005) or patients (Stern, 2002 ; Alchanatis et al., 2005) to maintain intact performances. The hypothesis of a reserve brain activation has been confirmed by functional imaging studies (fMRI) using cognitive tasks (Thomas et al., 2005 ; Ayalon et al., 2006a , 2009a , b ; Castronovo et al., 2009 ; Yaouhi et al., 2009 ; Zhang et al., 2011) showing a decrease in frontal cortex metabolism in the resting condition and an increase in neural activation in frontal lobe, cingulate, thalamus, and hippocampus during task activation.

Role of Hypoxemia

From large population studies (Telakivi et al., 1988 ; Jennum and Sjol, 1994 ; Kim et al., 1997 ; Redline et al., 1997 ; Horne, 1998 ; Engleman and Joffe, 1999 ; Adams et al., 2001 ; Beebe and Gozal, 2002) it would seem that, while the excessive daytime sleepiness and sleep fragmentation influences attention, the hypoxemia contributes to frontal impairment, and executive dysfunction. Using an experimental model of OSA (Gozal et al., 2001) in rats exposed for 2 weeks to intermittent hypoxia, the authors found a

neuronal loss or apoptosis indicating a greater vulnerability of the frontal lobe to hypoxemia. Moreover, Mc Coy et al. (2010) recently showed an impaired allocation of attentional resources in rats exposed one week to intermittent hypoxia. Since frontal lobes have dense connections to other cortical areas (Fulda and Schulz, 2001 ; Beebe and Gozal, 2002) the primary frontal dysfunction will progressively affect other brain regions, inducing more complex cognitive dysfunction. If so, the persistence of a neuropsychological deficit after CPAP (Bedard et al., 1993 ; Zimmermann et al., 1996 ; Lau et al., 2010 ; Antic et al., 2011 ; Matthews and Aloia, 2011) may be explained. However, if hypoxemia alone may explain the cognitive dysfunction in severe cases, in mildly affected patients (Redline et al., 1997 ; Lim and Veasey, 2010) the interacting effect of cognitive reserve (McCoy and Strecher, 2011), intelligence level (Quan et al., 2006), and depression (Sachs-Ericsson et al., 2005 ; Cross et al., 2008) needs to be considered.

Neuroimaging Data

Within the past decade, the growing prevalence of functional neuroimaging studies has induced an increased interest in the association between OSA and cognition and has opened a new window on the role of cerebral metabolic and circulatory impairment in neuropsychological dysfunction. Routine neuroimaging studies (MRI) in OSA patients have reported inconsistent findings (Davies et al., 2001) or silent vascular lesions (O'Donoghue et al., 2005 ; Nishibayashi et al., 2008) suggesting a general brain impairment. Voxel-based morphometry (Macey et al., 2002 , 2008) have demonstrated a gray matter reduction in brain regions that regulate memory and executive functions, i. e., cingulum, frontal, parietal and

temporal areas, and hippocampus. More sensitive techniques (Zimmermann and Aloia, 2006) such as spectroscopy (Kamba et al., 1997 ; O'Donoghue et al., 2012), functional MRI (Canessa et al., 2011), or positron emission tomography (PET; Morrell et al., 2003) have revealed functional alterations in specific brain areas implicated in cognitive function and affecting the prefrontal and the parieto-occipital cortex (Yaouhi et al., 2009) and the hippocampus (Torelli et al., 2011), the latter critical for memory. Interestingly, in the Yaouhi et al. (2009) study, the authors found that gray matter density and metabolic levels were altered even in patients without cognitive disturbances, suggesting that cerebral changes precede the onset of neuropsychological deficits. Canessa et al. (2011) performed a neuropsychological testing and voxel-based morphometry in 17 severely affected patients before and after 3-months of CPAP treatment. Prior to treatment the patients had poorer performances in some cognitive tests and a reduction of gray matter volume in the hippocampus, parietal cortex and frontal areas. After treatment there was an improvement in memory, attention and executive functions that paralleled the gray matter increase in the hippocampus and frontal areas, without, however, a complete normalization both in cognitive function and gray matter density. In contrast, a recent study using magnetic resonance spectroscopy (O'Donoghue et al., 2012) shows that OSA patients had decreased metabolic activity in the frontal lobe and hippocampus that did not correlate with cognitive scores and did not change after 6 months of CPAP therapy.

To date, any significant relationship between cognitive scores and brain morphological alteration has been reported, except for a slight association

between hippocampal gray matter decrease, and memory dysfunction (Yaouhi et al., 2009) and the gray matter increase in the left entorhinal cortex in patients showing a reduction of errors at the Stroop test (Canessa et al., 2011). The lack of significant relationship between morphological changes and neuropsychological scores may be explained by the interplay of compensatory mechanisms reflected by the increased activation of frontal areas and hippocampus in fMRI and PET studies (Castronovo et al., 2009 ; Yaouhi et al., 2009).

Cognitive Function in Elderly OSA Subjects

Although several studies have shown that the prevalence of OSA increases with age (Bixler et al., 1998 , 2001 ; Young et al., 2002) there is debate as to whether OSA phenotype in older adults is equal to that in middle-aged patients (Ancoli-Israel et al., 1991 ; Phillips et al., 1992 ; Bliwise, 1994 ; Young, 1996) and whether the aging *per se* increases the susceptibility to cognitive dysfunction (Alchanatis et al., 2008 ; Mathieu et al., 2008). A first epidemiological survey (Boland et al., 2002) has not revealed any evidence of a dose-response relationship between the respiratory disturbance index and cognitive function score in a cohort of 837 men and 923 women over 60 years old. Studies performed on sleep clinic patients have given conflicting results, some authors reporting a relationship between cognitive impairment and OSA (Kim et al., 1997 ; Cohen-Zion et al., 2001) in older patients, while others do not (Phillips et al., 1992). Severity of the disease seems to play a key role in cognitive deficit, older patients being more likely to have a cognitive deficit in attention and executive function when the AHI is greater than 30 (Aloia et al., 2004). In a prospective study conducted on 289

women aged 82 with mild cognitive impairment and dementia (Yaffe et al., 2011) the authors demonstrated that older OSA women had an increased risk of developing mild cognitive impairment or dementia after 5 years, stressing the key role of OSA in the increased cognitive risk. When treated, patients without (Aloia et al., 2003) or with mild dementia (Ancoli-Israel and Coy, 1994 ; Ayalon et al., 2006b ; Ancoli-Israel et al., 2008 ; Cooke et al., 2009) have a slower cognitive deterioration and sometimes even an improvement thus stressing the link between cognitive decline and OSA.

To explain the link between cognitive decline and OSA in the elderly, an emerging hypothesis is that the chronic intermittent hypoxemia observed in OSA patients might be seen as a factor which expedites the effects of other conditions, particularly aging, that are known to cause brain atrophy or damage in the prefrontal cortex and hippocampus. Ayalon et al. (2010) demonstrate that the presence of OSA accelerates the age-related decline in cognitive performances in middle-aged patients (> 45 years) showing a decreased activation of the frontal gyrus, hippocampus, and parietal lobe during a sustained attention and a verbal encoding task. These results are supported by a morphological study (Torelli et al., 2011) showing a correlation between age and volumes of the total and left hippocampus, amygdale, and brain parenchyma in OSA patients. If the presence of OSA can be seen as a factor which accelerates the process of brain aging, an early treatment should be proposed (Pack and Maislin, 2001 ; Ancoli-Israel, 2007) to prevent or to slow the cognitive deterioration (Cohen-Zion et al., 2001).

In summary, the connection between OSA and cognition, the increase of OSA risk in general population and the increasing aging population underline the

need of further studies on the risk of development of a cognitive impairment in OSA patients and on the long-term effect of therapy on the age-related cognitive decline.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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